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(21) International Application Number: PCT/US00/09688 (22) International Filing Date: 10 April 2000 (10.04.00) (30) Priority Data: 09/288,950 9 April 1999 (09.04.99) US 09/346,327 2 July 1999 (02.07.99) US (71) Applicant (for all designated States except US): CORIXA CORPORATION [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): REED, Steven, G. [US/US]; 2843 - 122nd Place NE, Bellevue, WA 98005 (US). XU, Jiangchun [US/US]; 15805 SE 43rd Place, Bellevue, WA 98006 (US). DILLON, Davin, C. [US/US]; 21607 NE 24th Street, Redmond, WA 98053 (US). (74) Agents: POTTER, Jane, E.R.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US) et al.			(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE (57) Abstract Compounds and methods for the treatment and diagnosis of breast cancer are provided. The inventive compounds include polypeptides containing at least a portion of a breast tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of breast cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.			

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COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

5 TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment and diagnosis of breast cancer. The invention is more particularly related to polypeptides comprising at least a portion of a protein that is preferentially expressed in breast tumor tissue and to polynucleotides encoding such polypeptides.

10 Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for treatment of breast cancer. Additionally such polypeptides and polynucleotides may be used in the immunodiagnosis of breast cancer.

BACKGROUND OF THE INVENTION

15 Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast
20 cancer are now one in eight.

No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) and aggressive treatment, which may include one or more of a variety of
25 treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. *See, e.g.,* Porter-Jordan and Lippman, *Breast Cancer* 8:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high

mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for therapy and diagnosis of breast cancer. The present invention fulfills these needs and
5 further provides other related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds and methods for immunotherapy of breast cancer. In one aspect, isolated polypeptides are provided
10 comprising at least an immunogenic portion of a breast tumor protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein the breast tumor protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-
15 97, 102 and 107, (b) complements of said nucleotide sequences and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. In specific embodiments, the isolated polypeptides of the present invention comprise an amino acid sequence of SEQ ID NO: 98, 99 or 101.

In related aspects, isolated polynucleotides encoding the above
20 polypeptides are provided. In specific embodiments, such polynucleotides comprise sequences provided in SEQ ID NOS: 3, 10, 17, 24, 45-52 and 55-67, 72, 73, 89-97, 102 and 107. The present invention further provides expression vectors comprising the above polynucleotides and host cells transformed or transfected with such expression vectors. In preferred embodiments, the host cells are selected from the
25 group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known breast antigen.

The present invention also provides pharmaceutical compositions
30 comprising at least one of the above polypeptides, or a polynucleotide encoding such a polypeptide, and a physiologically acceptable carrier, together with vaccines

comprising at least one or more such polypeptide or polynucleotide in combination with a non-specific immune response enhancer. Pharmaceutical compositions and vaccines comprising one or more of the above fusion proteins are also provided.

In related aspects, pharmaceutical compositions for the treatment of breast cancer comprising at least one polypeptide and a physiologically acceptable carrier are provided, wherein the polypeptide comprises an immunogenic portion of a breast tumor protein or a variant thereof, the breast tumor protein being encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106, (b) complements of said nucleotide sequences, and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. The invention also provides vaccines for the treatment of breast cancer comprising such polypeptides in combination with a non-specific immune response enhancer, together with pharmaceutical compositions and vaccines comprising at least one polynucleotide comprising a sequence provided in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106.

In yet another aspect, methods are provided for inhibiting the development of breast cancer in a patient, comprising administering an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

The present invention also provides methods for immunodiagnosis of breast cancer, together with kits for use in such methods. In one specific aspect of the present invention, methods are provided for detecting breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one

of the above polypeptides; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of breast cancer.

The present invention further provides methods for detecting breast cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

In a further aspect, the present invention provides a method for detecting breast cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein

are hereby incorporated by reference in their entirety as if each was incorporated individually.

5 BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figs. 1A and B show the specific lytic activity of a first and a second B511S-specific CTL clone, respectively, measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares).

- 10 SEQ ID NO: 1 is the determined 3'cDNA sequence of 1T-5120
SEQ ID NO: 2 is the determined 3'cDNA sequence of 1T-5122
SEQ ID NO: 3 is the determined 3'cDNA sequence of 1T-5123
SEQ ID NO: 4 is the determined 3'cDNA sequence of 1T-5125
SEQ ID NO: 5 is the determined 3'cDNA sequence of 1T-5126
15 SEQ ID NO: 6 is the determined 3'cDNA sequence of 1T-5127
SEQ ID NO: 7 is the determined 3'cDNA sequence of 1T-5129
SEQ ID NO: 8 is the determined 3'cDNA sequence of 1T-5130
SEQ ID NO: 9 is the determined 3'cDNA sequence of 1T-5133
SEQ ID NO: 10 is the determined 3'cDNA sequence of 1T-5136
20 SEQ ID NO: 11 is the determined 3'cDNA sequence of 1T-5137
SEQ ID NO: 12 is the determined 3'cDNA sequence of 1T-5139
SEQ ID NO: 13 is the determined 3'cDNA sequence of 1T-5142
SEQ ID NO: 14 is the determined 3'cDNA sequence of 1T-5143
SEQ ID NO: 15 is the determined 5'cDNA sequence of 1T-5120
25 SEQ ID NO: 16 is the determined 5'cDNA sequence of 1T-5122
SEQ ID NO: 17 is the determined 5'cDNA sequence of 1T-5123
SEQ ID NO: 18 is the determined 5'cDNA sequence of 1T-5125
SEQ ID NO: 19 is the determined 5'cDNA sequence of 1T-5126
SEQ ID NO: 20 is the determined 5'cDNA sequence of 1T-5127
30 SEQ ID NO: 21 is the determined 5'cDNA sequence of 1T-5129
SEQ ID NO: 22 is the determined 5'cDNA sequence of 1T-5130

- SEQ ID NO: 23 is the determined 5'cDNA sequence of 1T-5133
SEQ ID NO: 24 is the determined 5'cDNA sequence of 1T-5136
SEQ ID NO: 25 is the determined 5'cDNA sequence of 1T-5137
SEQ ID NO: 26 is the determined 5'cDNA sequence of 1T-5139
5 SEQ ID NO: 27 is the determined 5'cDNA sequence of 1T-5142
SEQ ID NO: 28 is the determined 5'cDNA sequence of 1T-5143
SEQ ID NO: 29 is the determined 5'cDNA sequence of 1D-4315
SEQ ID NO: 30 is the determined 5'cDNA sequence of 1D-4311
SEQ ID NO: 31 is the determined 5'cDNA sequence of 1E-4440
10 SEQ ID NO: 32 is the determined 5'cDNA sequence of 1E-4443
SEQ ID NO: 33 is the determined 5'cDNA sequence of 1D-4321
SEQ ID NO: 34 is the determined 5'cDNA sequence of 1D-4310
SEQ ID NO: 35 is the determined 5'cDNA sequence of 1D-4320
SEQ ID NO: 36 is the determined 5'cDNA sequence of 1E-4448
15 SEQ ID NO: 37 is the determined 5'cDNA sequence of 1S-5105
SEQ ID NO: 38 is the determined 5'cDNA sequence of 1S-5110
SEQ ID NO: 39 is the determined 5'cDNA sequence of 1S-5111
SEQ ID NO: 40 is the determined 5'cDNA sequence of 1S-5116
SEQ ID NO: 41 is the determined 5'cDNA sequence of 1S-5114
20 SEQ ID NO: 42 is the determined 5'cDNA sequence of 1S-5115
SEQ ID NO: 43 is the determined 5'cDNA sequence of 1S-5118
SEQ ID NO: 44 is the determined 5'cDNA sequence of 1T-5134
SEQ ID NO: 45 is the determined 5'cDNA sequence of 1E-4441
SEQ ID NO: 46 is the determined 5'cDNA sequence of 1E-4444
25 SEQ ID NO: 47 is the determined 5'cDNA sequence of 1E-4322
SEQ ID NO: 48 is the determined 5'cDNA sequence of 1S-5103
SEQ ID NO: 49 is the determined 5'cDNA sequence of 1S-5107
SEQ ID NO: 50 is the determined 5'cDNA sequence of 1S-5113
SEQ ID NO: 51 is the determined 5'cDNA sequence of 1S-5117
30 SEQ ID NO: 52 is the determined 5'cDNA sequence of 1S-5112

- SEQ ID NO: 53 is the determined cDNA sequence of 1013E11
- SEQ ID NO: 54 is the determined cDNA sequence of 1013H10
- SEQ ID NO: 55 is the determined cDNA sequence of 1017C2
- SEQ ID NO: 56 is the determined cDNA sequence of 1016F8
- 5 SEQ ID NO: 57 is the determined cDNA sequence of 1015F5
- SEQ ID NO: 58 is the determined cDNA sequence of 1017A11
- SEQ ID NO: 59 is the determined cDNA sequence of 1013A11
- SEQ ID NO: 60 is the determined cDNA sequence of 1016D8
- SEQ ID NO: 61 is the determined cDNA sequence of 1016D12
- 10 SEQ ID NO: 62 is the determined cDNA sequence of 1015E8
- SEQ ID NO: 63 is the determined cDNA sequence of 1015D11
- SEQ ID NO: 64 is the determined cDNA sequence of 1012H8
- SEQ ID NO: 65 is the determined cDNA sequence of 1013C8
- SEQ ID NO: 66 is the determined cDNA sequence of 1014B3
- 15 SEQ ID NO: 67 is the determined cDNA sequence of 1015B2
- SEQ ID NO: 68-71 are the determined cDNA sequences of previously identified antigens
- SEQ ID NO: 72 is the determined cDNA sequence of JJ9434
- SEQ ID NO: 73 is the determined cDNA sequence of B535S
- 20 SEQ ID NO: 74-88 are the determined cDNA sequence of previously identified antigens
- SEQ ID NO: 89 is the determined cDNA sequence of B534S
- SEQ ID NO: 90 is the determined cDNA sequence of B538S
- SEQ ID NO: 91 is the determined cDNA sequence of B542S
- 25 SEQ ID NO: 92 is the determined cDNA sequence of B543S
- SEQ ID NO: 93 is the determined cDNA sequence of P501S
- SEQ ID NO: 94 is the determined cDNA sequence of B541S
- SEQ ID NO: 95 is an extended cDNA sequence for 1016F8 (also referred to as B511S)
- 30 SEQ ID NO: 96 is an extended cDNA sequence for 1016D12 (also referred to as

B532S)

SEQ ID NO: 97 is an extended cDNA sequence for 1012H8 (also referred to as B533S)

SEQ ID NO: 98 is the predicted amino acid sequence for B511S

5 SEQ ID NO: 99 is the predicted amino acid sequence for B532S

SEQ ID NO: 100 is the determined full-length cDNA sequence for P501S

SEQ ID NO: 101 is the predicted amino acid sequence for P501S

SEQ ID NO: 102 is the determined cDNA sequence of clone #19605, also referred to as 1017C2, showing no significant homology to any known gene

10 SEQ ID NO: 103 is the determined 3' end cDNA sequence for clone #19599, showing homology to the Tumor Expression Enhanced gene

SEQ ID NO: 104 is the determined 5' end cDNA sequence for clone #19599, showing homology to the Tumor Expression Enhanced gene

15 SEQ ID NO: 105 is the determined cDNA sequence for clone #19607, showing homology to Stromelysin-3

SEQ ID NO: 106 is the determined cDNA sequence for clone #19601, showing homology to Collagen

SEQ ID NO: 107 is the determined cDNA sequence of clone #19606, also referred to as B546S, showing no significant homology to any known gene

20

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the immunotherapy and diagnosis of breast cancer. The inventive compositions are generally isolated polypeptides that comprise at least
25 a portion of a breast tumor protein. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In particular, the subject invention discloses isolated polypeptides comprising at least a portion of a human breast tumor protein, or a variant thereof,
30 wherein the breast tumor protein includes an amino acid sequence encoded by a

polynucleotide molecule including a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, the complements of said nucleotide sequences, and variants thereof. In certain specific embodiments, the inventive polypeptides comprise an amino acid sequence selected
5 from the group consisting of sequences provided in SEQ ID NO: 98, 99 and 101, and variants thereof. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above breast proteins may consist entirely of the portion, or the portion
10 may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may be immunoreactive and/or antigenic.

As used herein, an "immunogenic portion" of a human breast tumor protein is a portion that is capable of eliciting an immune response in a patient
15 inflicted with breast cancer and as such binds to antibodies present within sera from a breast cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays may generally be
20 performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the
25 immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of breast cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known

in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides. A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the therapeutic, antigenic and/or immunogenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the

following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA*, 2:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within

the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, more preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) *Unified Approach to Alignment and Phylogenies* pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad. Sci. USA* 80:726-730.

Preferably, the “percentage of sequence identity” is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Also included in the scope of the present invention are alleles of the genes encoding the nucleotide sequences recited herein. As used herein, an “allele” or “allelic sequence” is an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given gene may have none, one, or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone or in combination with the others, one or more times in a given sequence.

For breast tumor polypeptides with immunoreactive properties, variants may alternatively be identified by modifying the amino acid sequence of one of the above polypeptides, and evaluating the immunoreactivity of the modified polypeptide. For breast tumor polypeptides useful for the generation of diagnostic binding agents, a variant may be identified by evaluating a modified polypeptide for the ability to generate antibodies that detect the presence or absence of breast cancer. Such modified sequences may be prepared and tested using, for example, the representative procedures described herein.

The breast tumor proteins of the present invention, and polynucleotide molecules encoding such proteins, may be isolated from breast tumor tissue using any

of a variety of methods well known in the art. Polynucleotide sequences corresponding to a gene (or a portion thereof) encoding one of the inventive breast tumor proteins may be isolated from a breast tumor cDNA library using a subtraction technique as described in detail below. Examples of such DNA sequences are provided in SEQ ID NOS: 1- 97, 100 and 102-107. Partial polynucleotide sequences thus obtained may be used to design oligonucleotide primers for the amplification of full-length polynucleotide sequences in a polymerase chain reaction (PCR), using techniques well known in the art (see, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 10 1989). Once a polynucleotide sequence encoding a polypeptide is obtained, any of the above modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA*, 2:183, 1983).

The breast tumor polypeptides disclosed herein may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 15 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

25 Alternatively, any of the above polypeptides may be produced recombinantly by inserting a polynucleotide sequence that encodes the polypeptide into an expression vector and expressing the protein in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an 30

expression vector containing a polynucleotide molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as CHO cells. The polynucleotide sequences expressed in this manner may
5 encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary
10 sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

15 In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known breast tumor antigen, together with variants of such fusion proteins.

A polynucleotide sequence encoding a fusion protein of the present
20 invention is constructed using known recombinant DNA techniques to assemble separate polynucleotide sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a polynucleotide sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a polynucleotide sequence encoding the second polypeptide so that the reading frames
25 of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds
30 into its secondary and tertiary structures. Such a peptide linker sequence is

incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated polynucleotide sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of polynucleotides are located only 5' to the polynucleotide sequence encoding the first polypeptide. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the polynucleotide sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91 (1997)).

Polypeptides of the present invention that comprise an immunogenic portion of a breast tumor protein may generally be used for immunotherapy of breast cancer, wherein the polypeptide stimulates the patient's own immune response to breast tumor cells. In further aspects, the present invention provides methods for using one or more of the immunoreactive polypeptides encoded by a polynucleotide

molecule having a sequence provided in SEQ ID NOS: 1- 97, 100 and 102-107 (or fusion proteins comprising one or more such polypeptides and/or polynucleotides encoding such polypeptides) for immunotherapy of breast cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease. Accordingly, the above immunoreactive polypeptides (or fusion proteins or polynucleotide molecules encoding such polypeptides) may be used to treat breast cancer or to inhibit the development of breast cancer. In a preferred embodiment, the polypeptides are administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the polypeptide or fusion protein is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more of such polypeptides and a non-specific immune response enhancer, wherein the non-specific immune response enhancer is capable of eliciting or enhancing an immune response to an exogenous antigen. Examples of non-specific-immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of breast tumor antigens, either incorporated into a combination polypeptide (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain polynucleotides encoding one or more of the above polypeptides, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems

contain the necessary polynucleotide sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a breast tumor cell antigen on its cell surface. In a preferred embodiment, the polynucleotide molecules may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *PNAS* 91:215-219, 1994; Kass-Eisler et al., *PNAS* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating polynucleotides into such expression systems are well known to those of ordinary skill in the art.

The polynucleotides may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science* 259:1745-1749, 1993, reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked polynucleotides may be increased by coating the polynucleotides onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or polynucleotide that is

effective to raise an immune response (cellular and/or humoral) against breast tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the polynucleotide in a dose) ranges from about 1 pg to about 5 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 µg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of 10 carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium 15 carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of non-specific immune response enhancers may be 20 employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's 25 Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active 30 immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host

immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

In passive immunotherapy, treatment involves the delivery of biologic
5 reagents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, gamma/delta T lymphocytes, tumor-infiltrating lymphocytes), killer cells (such as
10 Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for
15 adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. These *in vitro* culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above,
20 the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B-cells, may be pulsed with immunoreactive polypeptides or polynucleotide sequence(s) may be introduced into antigen presenting
25 cells, using standard techniques well known in the art. For example, antigen presenting cells may be transfected or transduced with a polynucleotide sequence, wherein said sequence contains a promoter region appropriate for inducing expression, and can be expressed as part of a recombinant virus or other expression system. Several viral vectors may be used to transduce an antigen presenting cell,
30 including pox virus, vaccinia virus, and adenovirus. Antigen presenting cells may be

transfected with polynucleotide sequences disclosed herein by a variety of means, including gene-gun technology, lipid-mediated delivery, electroporation, osmotic shock, and particulate delivery mechanisms, resulting in efficient and acceptable expression levels as determined by one of ordinary skill in the art. For cultured T-
5 cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term *in vivo*. Studies have demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever, M., et al, "Therapy With Cultured T Cells: Principles Revisited,"
10 *Immunological Reviews*, 157:177, 1997).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the
15 disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective
20 *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. (*Crit. Rev. Oncol. Hematol.*, 22(3), 213, 1996). Cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system. The separated cells are stimulated
25 with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

In other embodiments, T-cell and/or antibody receptors specific for the
30 polypeptides can be cloned, expanded, and transferred into other vectors or effector

cells for use in adoptive immunotherapy. In particular, T cells may be transfected with the appropriate genes to express the variable domains from tumor specific monoclonal antibodies as the extracellular recognition elements and joined to the T cell receptor signaling chains, resulting in T cell activation, specific lysis, and cytokine release. This enables the T cell to redirect its specificity in an MHC-independent manner. See for example, Eshhar, Z., *Cancer Immunol Immunother*, 45(3-4):131-6, 1997 and Hwu, P., et al, *Cancer Res*, 55(15):3369-73, 1995. Another embodiment may include the transfection of tumor antigen specific alpha and beta T cell receptor chains into alternate T cells, as in Cole, DJ, et al, *Cancer Res*, 55(4):748-52, 1995.

In further embodiments, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al. (*Immunological Reviews*, 157:177, 1997).

Additionally, vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

In one specific embodiment, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

Polypeptides of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human breast tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without breast cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a breast tumor protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic breast cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic breast cancer. Suitable portions of such breast tumor proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic breast cancer in substantially all (*i.e.*, at least about 80%, and preferably at least about 90%) of the patients for which breast cancer would be indicated using the full length protein, and that indicate the absence of breast cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human breast tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human breast tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic breast cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic breast tumors by such procedures are

considered to be useful in assays for detecting primary or metastatic human breast tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human breast tumors may be used as markers for diagnosing breast cancer or for monitoring disease progression in patients. In one embodiment, breast cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera and urine.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding
5 partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled
10 with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill
15 in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S.
20 Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the
25 antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour
30 and about 1 day. In general, contacting a well of a plastic microtiter plate (such as

polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally
5 be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by
10 condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the
15 sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a
20 method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The
25 immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast
30 cancer. Preferably, the contact time is sufficient to achieve a level of binding that is

at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about
5 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase),
10 substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound
15 polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or
20 autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time),
25 followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the
30 immobilized antibody is incubated with samples from patients without breast cancer.

In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for breast cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for breast cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of breast cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level

of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of breast cancer. In this embodiment, assays as described above for the diagnosis of breast cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, breast cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, breast cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may

then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate breast tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides,

differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, 5 diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a 10 substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an 15 antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on 20 agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino 25 groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a 30 linker group which is cleavable during or upon internalization into a cell. A number

of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous,

intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

5 Diagnostic reagents of the present invention may also comprise at least a portion of a polynucleotide disclosed herein. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify breast tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide
10 encoding a breast tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a breast tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a
15 biological sample.

 As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question, or an oligonucleotide sequence that is anti-sense to a
20 sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10
25 contiguous nucleotides of a polynucleotide disclosed herein or that is anti-sense to a polynucleotide sequence disclosed herein. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide that encodes one of the polypeptides disclosed herein or that is anti-sense to a sequence that encodes one of the polypeptides
30 disclosed herein. Techniques for both PCR based assays and hybridization assays are

well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect breast tumor-specific sequences in biological samples, including blood, urine and/or breast tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES

This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

A human breast tumor cDNA expression library was constructed from a pool of breast tumor poly A⁺ RNA from three patients using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, breast tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BstX I adaptors (Invitrogen, Carlsbad, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA 94303), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen, Carlsbad, CA) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human breast cDNA expression library was prepared from a pool of four normal breast tissue specimens. The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The breast tumor library contained 1.14×10^7 independent colonies, with more than 90% of clones having a visible insert and the average insert size being 936 base pairs. The normal breast cDNA library contained 6×10^6 independent colonies, with 83% of clones having inserts and the average insert size being 1015 base pairs. Sequencing analysis showed both libraries to contain good complex cDNA clones that were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination sequencing.

cDNA library subtraction was performed using the above breast tumor and normal breast cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a breast tumor-specific subtracted cDNA library was generated as follows. Normal breast cDNA library (70 μ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μ l of H₂O, heat-denatured and mixed with 100 μ l (100 μ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA), the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μ l H₂O to form the driver DNA.

To form the tracer DNA, 10 μ g breast tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μ l H₂O. Tracer DNA was mixed with 15 μ l driver DNA and 20 μ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and

incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μ l H₂O, mixed with 8 μ l driver DNA and 20 μ l of 2 x hybridization buffer, and
5 subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK⁺ (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a breast tumor specific subtracted cDNA library.

10 To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted breast tumor specific library and characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Thirty-eight distinct cDNA clones were found in the subtracted breast tumor-specific cDNA
15 library. The determined 3' cDNA sequences for 14 of these clones are provided in SEQ ID NO: 1-14, with the corresponding 5' cDNA sequences being provided in SEQ ID NO: 15-28, respectively. The determined one strand (5' or 3') cDNA sequences for the remaining clones are provided in SEQ ID NO: 29-52. Comparison
20 of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences provided in SEQ ID NO: 3, 10, 17, 24 and 45-52. The sequences provided in SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-41, 43 and 44 were found to show at least some degree of homology to known human genes. The sequence of SEQ ID NO: 42
was found to show some homology to a known yeast gene.

25 cDNA clones isolated in the breast subtraction described above were colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Fremont, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array.
30 mRNA was extracted from the tissue sample to be tested, reverse transcribed, and

fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity.

Data was analyzed using GEMTOOLS Software. Twenty one distinct
5 cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested. The determined partial cDNA sequences for these clones are provided in SEQ ID NO: 53-73. Comparison of the sequences of SEQ ID NO: 53, 54 and 68-71 with those in the gene bank as described above, revealed some homology to previously identified human genes. No significant homologies were
10 found to the sequences of SEQ ID NO: 55-67, 72 (referred to as JJ 9434) and 73 (referred to as B535S). In further studies, full length cDNA sequences were obtained for the clones 1016F8 (SEQ ID NO: 56; also referred to as B511S) and 1016D12 (SEQ ID NO: 61; also referred to as B532S), and an extended cDNA sequence was obtained for 1012H8 (SEQ ID NO: 64; also referred to as B533S). These cDNA
15 sequences are provided in SEQ ID NO: 95-97, respectively, with the corresponding predicted amino acid sequences for B511S and B532S being provided in SEQ ID NO: 98 and 99, respectively.

Analysis of the expression of B511S in breast tumor tissues and in a variety of normal tissues (skin, PBMC, intestine, breast, stomach, liver, kidney, fetal
20 tissue, adrenal gland, salivary gland, spinal cord, large intestine, small intestine, bone marrow, brain, heart, colon and pancreas) by microarray, northern analysis and real time PCR, demonstrated that B511S is over-expressed in breast tumors, and normal breast, skin and salivary gland, with expression being low or undetectable in all other tissues tested.

25 Analysis of the expression of B532S in breast tumor tissue and in a variety of normal tissues (breast, PBMC, esophagus, HMEC, spinal cord, bone, thymus, brain, bladder, colon, liver, lung, skin, small intestine, stomach, skeletal muscle, pancreas, aorta, heart, spleen, kidney, salivary gland, bone marrow and adrenal gland) by microarray, Northern analysis and real time PCR, demonstrated that

B532S is over-expressed in 20-30% of breast tumors with expression being low or undetectable in all other tissues tested.

In a further experiment, cDNA fragments were obtained from two subtraction libraries derived by conventional subtraction, as described above and
5 analyzed by DNA microarray. In one instance the tester was derived from primary breast tumors, referred to as Breast Subtraction 2, or BS2. In the second instance, a metastatic breast tumor was employed as the tester, referred to as Breast Subtraction 3, or BS3. Drivers consisted of normal breast.

cDNA fragments from these two libraries were submitted as templates
10 for DNA microarray analysis, as described above. DNA chips were analyzed by hybridizing with fluorescent probes derived from mRNA from both tumor and normal tissues. Analysis of the data was accomplished by creating three groups from the sets of probes, referred to as breast tumor/mets, normal non-breast tissues, and metastatic breast tumors. Two comparisons were performed using the modified Gemtools
15 analysis. The first comparison was to identify templates with elevated expression in breast tumors. The second was to identify templates not recovered in the first comparison that yielded elevated expression in metastatic breast tumors. An arbitrary level of increased expression (mean of tumor expression versus the mean of normal tissue expression) was set at approximately 2.2.

20 In the first round of comparison to identify over-expression in breast tumors, two novel gene sequences were identified, hereinafter referred to as B534S and B538S (SEQ ID NO: 89 and 90, respectively), together with six sequences that showed some degree of homology to previously identified genes (SEQ ID NO: 74-79). The sequences of SEQ ID NO: 75 and 76 were subsequently determined to be
25 portions of B535S (SEQ ID NO: 73). In a second comparison to identify elevated expression in metastatic breast tumors, five novel sequences were identified, hereinafter referred to as B535S, B542S, B543S, P501S and B541S (SEQ ID NO: 73 and 91-94, respectively), as well as nine gene sequences that showed some homology to known genes (SEQ ID NO: 80-88). Clone B534S and B538S (SEQ ID NO: 89 and

90) were shown to be over-expressed in both breast tumors and metastatic breast tumors.

In a subsequent series of studies, 457 clones from Breast Subtraction 2 were analyzed by microarray on Breast Chip 3. As described above, a first comparison to identify over-expression in breast tumors over normal non-breast tissues was performed. This analysis yielded six cDNA clones that demonstrated elevated expression in breast tumor over normal non-breast tissues. Two of these clones, referred to as 1017C2 (SEQ ID NO: 102) and B546S (SEQ ID NO: 107) do not share significant homology to any known genes. Clone B511S also showed over-expression in breast tumor, which was previously described as 1016F8, with the determined cDNA sequence provided in SEQ ID NO: 95 and the predicted amino acid sequence provided in SEQ ID NO: 98. The remaining four clones over-expressed in breast tumor were found to share some degree of homology to Tumor Expression Enhanced Gene (SEQ ID NO: 103 and 104) Stromelysin-3 (SEQ ID NO: 105) or Collagen (SEQ ID NO: 106).

In the second comparison to determine genes with elevated expression in metastatic breast tumors over non-breast normal tissues, a profile similar to the first comparison was derived. The two putatively novel clones, 1017C2 and B546S, SEQ ID NO: 102 and 107, respectively, were overexpressed in metastatic breast tumors. In addition, Tumor Expression Enhanced Gene and B511S also showed elevated expression in metastatic breast tumors.

As described in U.S. Patent Application No. 08/806,099, filed February 25, 1997, the antigen P501S was isolated by subtracting a prostate tumor cDNA library with a normal pancreas cDNA library and with three genes found to be abundant in a previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. The determined full-length cDNA sequence for P501S is provided in SEQ ID NO: 100, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 101. Expression of P501S in breast tumor was examined by microarray analysis. Over-expression was found in prostate tumor, breast tumor

and metastatic breast tumor, with negligible to low expression being seen in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

5

Example 2

GENERATION OF HUMAN CD8+ CYTOTOXIC T-CELLS THAT RECOGNIZE ANTIGEN PRESENTING CELLS EXPRESSING BREAST TUMOR ANTIGENS

10 This Example illustrates the generation of T cells that recognize target cells expressing the antigen B511S, also known as 1016-F8 (SEQ ID NO: 56). Human CD8+ T cells were primed *in-vitro* to the B511S gene product using dendritic cells infected with a recombinant vaccinia virus engineered to express B511S as follows (also see Yee et al., Journal of Immunology (1996) 157 (9):4079-86).

15 Dendritic cells (DC) were generated from peripheral blood derived monocytes by differentiation for 5 days in the presence of 50 µg/ml GMCSF and 30 µg/ml IL-4. DC were harvested, plated in wells of a 24-well plate at a density of 2×10^5 cells/well and infected for 12 hours with B511S expressing vaccinia at a multiplicity of infection of 5. DC were then matured overnight by the addition of 3 µg/ml CD40-

20 Ligand and UV irradiated at 100µW for 10 minutes. CD8+ T cells were isolated using magnetic beads, and priming cultures were initiated in individual wells (typically in 24 wells of a 24-well plate) using 7×10^5 CD8+ T cells and 1×10^6 irradiated CD8-depleted PBMC. IL-7 at 10 ng/ml was added to cultures at day 1. Cultures were re-stimulated every 7-10 days using autologous primary fibroblasts

25 retrovirally transduced with B511S and the costimulatory molecule B7.1. Cultures were supplemented at day 1 with 15 I.U. of IL-2. Following 4 such stimulation cycles, CD8+ cultures were tested for their ability to specifically recognize autologous fibroblasts transduced with B511S using an interferon-γ Elispot assay (see Lalvani et al J. Experimental Medicine (1997) 186:859-965). Briefly, T cells from

30 individual microcultures were added to 96-well Elispot plates that contained autologous fibroblasts transduced to express either B511S or as a negative control

antigen EGFP, and incubated overnight at 37° C; wells also contained IL-12 at 10 ng/ml. Cultures were identified that specifically produced interferon- γ only in response to B511S transduced fibroblasts; such lines were further expanded and also cloned by limiting dilution on autologous B-LCL retrovirally transduced with B511S.

- 5 Lines and clones were identified that could specifically recognize autologous B-LCL transduced with B511S but not autologous B-LCL transduced with the control antigens EGFP or HLA-A3. An example demonstrating the ability of human CTL cell lines derived from such experiments to specifically recognize and lyse B511S expressing targets is presented in Figure 1.

10

Example 3

SYNTHESIS OF POLYPEPTIDES

- Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using
- 20 the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60%
- 25 acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

1. An isolated polypeptide comprising an immunogenic portion of a breast protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.
2. The isolated polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 98,99 and 101.
3. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of any one of claims 1 and 2.
4. An isolated polynucleotide comprising a sequence provided in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107.
5. An expression vector comprising a polynucleotide according to any one of claims 3 and 4.
6. A host cell transformed with the expression vector of claim 5.
7. The host cell of claim 6 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.
8. A pharmaceutical composition comprising the polypeptide of claim 1 and a physiologically acceptable carrier.
9. A vaccine comprising the polypeptide of claim 1 and a non-specific immune response enhancer.

10. The vaccine of claim 9 wherein the non-specific immune response enhancer is an adjuvant.

11. A vaccine comprising an isolated polynucleotide of any one of claims 3 and 4, and a non-specific immune response enhancer.

12. The vaccine of claim 11 wherein the non-specific immune response enhancer is an adjuvant.

13. A pharmaceutical composition for the treatment of breast cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

14. A vaccine for the treatment of breast cancer comprising a polypeptide and a non-specific immune response enhancer, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

15. The vaccine of claim 14 wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine for the treatment of breast cancer comprising a polynucleotide and a non-specific immune response enhancer, the polynucleotide

comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

17. The vaccine of claim 16, wherein the non-specific immune response enhancer is an adjuvant.

18. A pharmaceutical composition according to any one of claims 8 and 13, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

19. A vaccine according to any one of claims 9, 11, 14 or 16, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

20. A fusion protein comprising at least one polypeptide according to claim 1.

21. A pharmaceutical composition comprising a fusion protein according to claim 20 and a physiologically acceptable carrier.

22. A vaccine comprising a fusion protein according to claim 20 and a non-specific immune response enhancer.

23. The vaccine of claim 22 wherein the non-specific immune response enhancer is an adjuvant.

24. A pharmaceutical composition according to claim 21, for use in manufacture of a medicament for inhibiting the development of breast cancer in a patient.

25. A vaccine according to claim 22, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

26. A method for detecting breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting breast cancer in the patient.

27. The method of claim 26 wherein the binding agent is a monoclonal antibody.

28. The method of claim 27 wherein the binding agent is a polyclonal antibody.

29. A method for monitoring the progression of breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

- (c) repeating steps (a) and (b); and
- (d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of breast cancer in the patient.

30. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a breast protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

31. A monoclonal antibody according to claim 30, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

32. The monoclonal antibody of claim 31 wherein the monoclonal antibody is conjugated to a therapeutic agent.

33. A method for detecting breast cancer in a patient comprising:

- (a) contacting a biological sample from a patient with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and
- (b) detecting in the sample a polynucleotide sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting breast cancer.

34. The method of claim 33, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NOS: 1-97, 100 and 102-107.

35. A diagnostic kit comprising:

- (a) one or more monoclonal antibodies of claim 30; and
- (b) a detection reagent.

36. A diagnostic kit comprising:

- (a) one or more monoclonal antibodies that bind to a polypeptide encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106, complements of said sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 or 103-106 under moderately stringent conditions; and
- (b) a detection reagent.

37. The kit of claims 35 or 36 wherein the monoclonal antibodies are immobilized on a solid support.

38. The kit of claim 37 wherein the solid support comprises nitrocellulose, latex or a plastic material.

39. The kit of claims 35 or 36 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

40. The kit of claim 39 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

41. The kit of claim 39 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

42. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107 complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions.

43. A diagnostic kit of claim 42 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NOS: 1-97, 100 and 102-107.

44. A method for detecting breast cancer in a patient, comprising:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and
- (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe, thereby detecting breast cancer in the patient.

45. The method of claim 44 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

46. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions.

47. The diagnostic kit of claim 46, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

48. A method for treating breast cancer in a patient, comprising the steps of:

- (a) obtaining peripheral blood cells from the patient;
- (b) incubating the cells in the presence of at least one polypeptide of any one of claims 1 and 2, such that T cells proliferate; and administering the proliferated T cells to the patient.

49. A method for treating breast cancer in a patient, comprising the steps of:

- (a) obtaining peripheral blood cells from the patient;
- (b) incubating the cells in the presence of at least one polynucleotide of any one of claims 3 and 4, such that T cells proliferate; and
- (c) administering the proliferated T cells to the patient.

50. The method of any one of claims 48 and 49 wherein the step of incubating the cells is repeated one or more times.

51. The method of any one of claims 48 and 49 wherein step (a) further comprises separating the T cells from the peripheral blood cells and the cells incubated in step (b) are the T cells.

52. The method of any one of claims 48 and 49 wherein step (a) further comprises separating CD4+ cells or CD8+ cells from the peripheral blood cells and the cells proliferated in step (b) are CD4+ or CD8+ T cells.

53. The method of any one of claims 48 and 49 wherein step (b) further comprises cloning at least one T cell that proliferated in the presence of the polypeptide.

54. A composition for the treatment of breast cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of any one of claims 1 and 2, in combination with a pharmaceutically acceptable carrier.

55. A composition for the treatment of breast cancer in a patient comprising T cells proliferated in the presence of a polynucleotide of any one of claims 3 and 4, in combination with a pharmaceutically acceptable carrier.

56. A method for treating breast cancer in a patient, comprising the steps of:

- (a) incubating antigen presenting cells in the presence of at least one polypeptide of any one of claims 1 and 2; and
- (b) administering to the patient the incubated antigen presenting cells.

57. A method for treating breast cancer in a patient, comprising the steps of:

- (a) incubating antigen presenting cells in the presence of at least one polynucleotide of any one of claims 3 and 4; and
- (b) administering to the patient the incubated antigen presenting

cells.

58. The method of claims 56 or 57 wherein the antigen presenting cells are selected from the group consisting of dendritic cells, macrophage cells, monocyte cells, fibroblast cells, B-cells or combinations thereof.

59. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of any one of claims 1 and 2, in combination with a pharmaceutically acceptable carrier.

60. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of any one of claims 3 and 4, in combination with a pharmaceutically acceptable carrier.

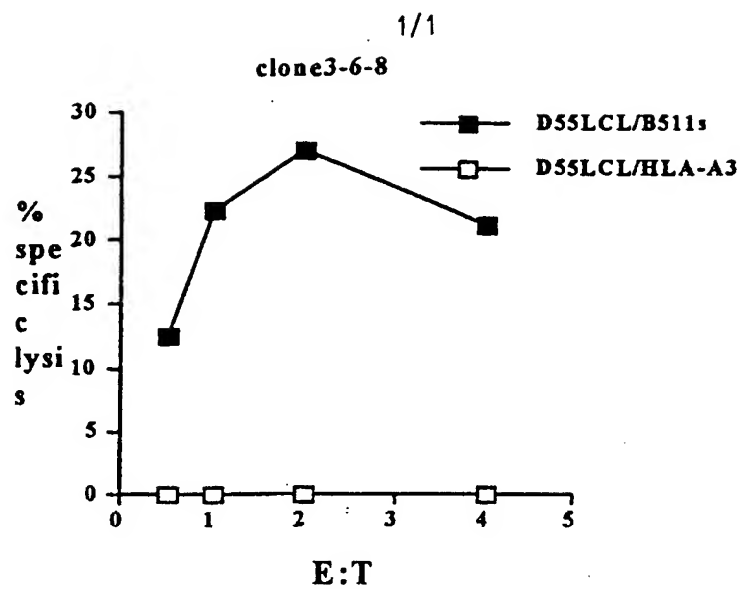


FIGURE 1A

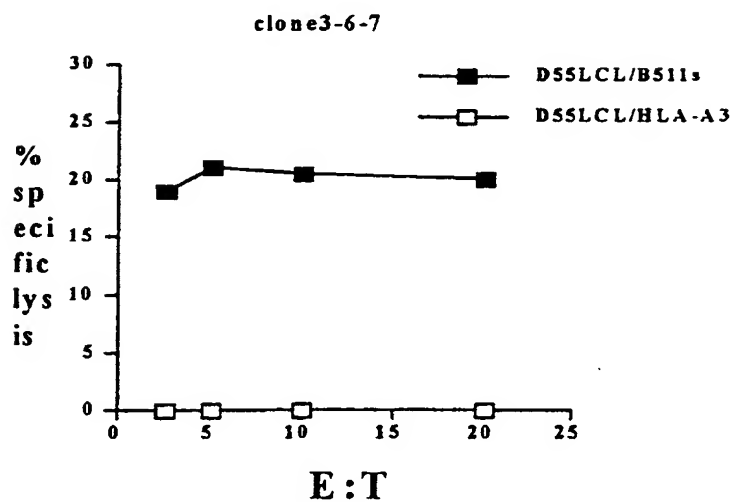


FIGURE 1B

Figure 1: Specific lytic activity of B511s-specific CTL clones 3-6-8 and 3-6-7 measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares). Each data point is the average of triplicate measurements.

SEQUENCE LISTING

<110> Corixa Corporation
 Reed, Steven G.
 Xu, Jiangchun
 Dillon, Davin C.

<120> COMPOUNDS FOR IMMUNOTHERAPY AND
 DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

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cctccnaata aaaatnccng gccctactgg gttaagcaac attgcatntc taaagaaacc    300
acatgcanac nagttaaacc tgtgnactgg tcangcaaac cnanntggaa nanaagggnn    360
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<400> 21
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ctacaatggg aaaatccata cataagtcag ttacttcctn atgagctttc tccttctgaa 120
tcctttatct tctgaagaaa gtacacacct tggtnatgat atcttttgaat tgcctttctt 180
tccaggcatc agttggatga ttcacatgg taattatggc attatcatat tcttcatact 240
tgtcatacga aaacaccagt tctgcccna gatgagcttg ttctgcagct cttagcacct 300
tggaatatatt cactctagac cagaaacagc tcccgggtgct ccctcatttt ctgaggctta 360
aattn 366

<210> 22
<211> 315
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(315)
<223> n = A,T,C or G

<400> 22
acttaatgca atctctggag gataatttgg atcaagaaat aaagaanaaa tgaattagga 60
gaagaaatna ctgggnata tttcaatatt ttagaacttt aanaatggtg actatgattt 120
caatatattt gtnaaaactg agatacangt ttgacctata tctgcatttt gataattaa 180
cnaatnnatt ctatttnaat gttgtttcag agtcacagca cagactgaaa ctttttttga 240
atacctnaat atcacacttn tnccttnaat gatgttgaag acaatgatga catgccttna 300
gcatataatg tcgac 315

<210> 23

<211> 202
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(202)
 <223> n = A,T,C or G

<400> 23
 actaatccag tgtggtgnaa ttccattgtg ttgggcaact caggatatta aatttatnat 60
 ttaaaaattc ccaagagaaa naaactccag gccctgattg tttcactggg gaattttacc 120
 aaatgttnca nnaaganatg acgctgattc tgtnaaatct ttttcagaag atagaggaga 180
 acaccaccg nttcatttta tg 202

<210> 24
 <211> 365
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(365)
 <223> n = A,T,C or G

<400> 24
 ggattttcttg cctttttctc cctttttaag tatcaatgta tgaaatccac ctgtaccacc 60
 ctttctgcca tacaaccgct accacatctg gtcctagaa cctgttttgc tttcatagat 120
 ggatctcgga accnagtgtt nacttcattt ttaaacccca ttttagcaga tngtttgctn 180
 tggctgtct gtattcacca tggggcctgt acacaccacg tgtggttata gtcaaacaca 240
 gtgccctcca ttgtggccac atgggagacc catnaccna tactgcatcc tgggctgatn 300
 acggcactgc atctnaccg acntgggatt gaaccggggg tgggcagcng aattgaacag 360
 gatca 365

<210> 25
 <211> 359
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(359)
 <223> n = A,T,C or G

<400> 25
 gtttcttgct tcaacagtgc ttggacggaa cccggcgctc gttccccacc ccggccggcc 60
 gcccatagcc agcctccgt cacctcttca ccgcaccctc ggactgcccc aaggcccccg 120
 ccgcncctcc ngcgccnccg agccaccgcc gccnccncca cctctccttn gtcccgcctc 180
 nacaacgcgt ccacctcgca ngttcgccng aactaccacc nggactcata ngccgcctc 240
 aaccgccccg tcaacctgga gctctncccc ccgacnttaa cctttccntg tcttacttac 300
 nttaacgcc gnttatcttg cttnaaaaga acttttcccc aatactttct ttcacnnt 359

<210> 26
 <211> 400
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(400)

<223> n = A,T,C or G

<400> 26

agtgaacag	tatatgtgaa	aaggagtttg	tgannagcta	cataaaaata	ttagatatct	60
ttataatttc	caataggata	ctcatcagtt	ttgaataana	gacatattct	agagaaacca	120
ggtttctggt	ttcagatttg	aactctcaag	agcttggaag	ttatcactcc	catcctcacg	180
acnacnaana	aatctnaacn	aacngaana	caatgacttt	tcttagatct	gtcaaagaac	240
ttcagccacg	aggaaaacta	tcnccctnaa	tactggggac	tggaaagaga	gggtacagag	300
aatcacagtg	aatcatagcc	caagatcagc	ttgcccggag	ctnaagctng	tacgatnatt	360
acttacaggg	accacttcac	agtnngtnga	tnaantgccn			400

<210> 27

<211> 366

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(366)

<223> n = A,T,C or G

<400> 27

gaattttctta	gaaactgaag	tttactctgt	tccaagatat	atcttcactg	tcttaaatcaa	60
agggcgctng	aatcatagca	aatattctca	tctttcaact	aactttaagt	agttntcctg	120
gaattttaca	ttttccagaa	aacactcctt	tctgtatctg	tgaaagaaag	tgtgcctcag	180
gctgtagact	gggctgcact	ggacacctgc	gggggactct	ggctnagtgn	ggacatggtc	240
agtattgatt	ttcctcanac	tcagcctgtg	tagctntgaa	agcatggaac	agattacact	300
gcagttnacg	tcatcccaca	catcttggac	tccnagacc	ggggagggtca	catagtcctg	360
tatgna						366

<210> 28

<211> 402

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(402)

<223> n = A,T,C or G

<400> 28

agtgggagcc	tcctccttcc	ccactcagtt	ctttacatcc	ccgaggcgca	gctgggcnaa	60
ggaagtggcc	agctgcagcg	cctcctgcag	gcagccaacg	ttcttgcttg	tggcctgtgc	120
agacacatcc	ttgccaccac	ctttaccgtc	catcangcct	gacacctgct	gcacccactc	180
gctngctttt	aagcccgat	nggctgcatt	ctgggggact	tgacacaggc	ncgtgatctt	240
gccagcctca	ttgtccaccg	tgaagagcat	ggcaaaaagt	ctgaggggag	tgcatcttga	300
anagcttcaa	ggcttcattc	agggccttng	ctnaggcgcc	nctctccatc	tccnggaata	360
acnagaggct	ggtnnnggtn	actntcaata	aactgcttcg	tc		402

<210> 29

<211> 175

<212> DNA

<213> Homo sapien

<400> 29

cggacgggca tgaccgggtcc ggtcagctgg gtggccagtt tcagttcttc agcagaactg	60
tctcccttct tgggggcccga gggcttctg gggaagagga tgagtttgga gcggtactcc	120
ttcagccgct gcacgttggg ctgcaggac tccgtggact tgttccgcct cctcg	175

<210> 30

<211> 360

<212> DNA

<213> Homo sapien

<400> 30

ttgtatttct tatgatctct gatgggttct tctcgaaaat gccaaagtga agactttgtg	60
gcatgctcca gatttaaate cagctgaggg tccctttgtt ttcagtcca tgtaacaatc	120
tggaaggaaa cttcacggac aggaagactg ctggagaaga gaagcgtgtt agccatttg	180
aggtctgggg aatcatgtaa agggtaacca gacctactt ttagttattt acatcaatga	240
gttctttcag ggaaccaaac ccagaattcg gtgcaaaagc caaacatctt ggtgggattt	300
gataaatgcc ttgggacctg gagtgtctggg cttgtgcaca ggaagagcac cagccgctga	360

<210> 31

<211> 380

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(380)

<223> n = A,T,C or G

<400> 31

acgctctaag cctgtccacg agctcaatag ggaagcctgt gatgactaca gactttgcga	60
acgctacgcc atggtttatg gatacaatgc tgcctataan cgctacttca ggaagcgccg	120
agggaccnaa tgagactgag ggaagaaaaa aaatctcttt ttttctggag gctggcacct	180
gattttgtat cccctgttnn cagcattncn gaaatacata ggcttatata caatgcttct	240
ttcctgtata ttctctgtgc tggctgcacc ccttnttccc gccccagat tgataagtaa	300
tgaaagtgca ctgcagtnag ggtcaangga gactcancat atgtgattgt tccntnataa	360
acttctggtg tgatactttc	380

<210> 32

<211> 440

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(440)

<223> n = A,T,C or G

<400> 32

gtgtatggga gccctgact cctcacgtgc ctgatctgtg cccttgggtcc caggtcaggc	60
ccaccccttg cacctccacc tgccccagcc cctgcctctg cccaagtgg ggccagctgc	120
cctcacttct ggggtggatg atgtgacctt cctnggggga ctgcggaagg gacaagggtt	180

```

ccctgaagtc ttacgggtcca acatcaggac caagtcccat ggacatgctg acaggggtccc      240
caggggagac cgtntcanta gggatgtgtg cctggctgtg tacgtgggtg tgcagtgcac      300
gtganaagca cgtggcggct tctggggggc atgtttgggg aaggaagtgt gccnccacc      360
cttgagaaac ctcagtcccn gtagccccct gccctggcac agcngcatnc acttcaaggg      420
caccctttgg gggttggggt

```

```

<210> 33
<211> 345
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(345)
<223> n = A,T,C or G

```

```

<400> 33
tattttaaca atgtttatta ttcatttatc cctctataga accaccaccc acaccgagga      60
gattatttgg agtgggtccc aacctagggc ctggactctg aaatctaact cccacttcc      120
ctcattttgt gacttaggtg ggggcatggt tcagtcagaa ctggtgtctc ctattggatc      180
gtgcagaagg aggacctagg cacacacata tgggtggccac acccaggagg gttgattggc      240
aggctggaag acaaaagtct cccaataaag gcacttttac ctcaaagang ggggtgggagt      300
tggtctgctg ggaatgttgt tgttgggggt gggaagantt atttc

```

```

<210> 34
<211> 440
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

```

```

<400> 34
tgtaattttt ttattgaaa acaaataaac aacttggaaat ggattttgag gcaaattgtg      60
ccataagcag attttaagt gctaaacaaa gtttaaaaag caagtaacaa taaaagaaaa      120
tgtttctggt acaggaccag cagtacaaaa aaatagtgtg cgagtacctg gataatacac      180
ccgttttgca atagtgaac ttttaagtac atattgttga ctgtccatag tccacgcaga      240
gttacaactc cacacttcaa caacaacatg ctgacagttc cttaaagaaaa ctactttaa      300
aaaggcataa cccagatgtt ccctcatttg accaactcca tctnagttta gatgtgcaga      360
agggttanaa ttttccaga gtaagccnca tgcaacatgt tacttgatca attttctaaa      420
ataaggtttt aggacaatga

```

```

<210> 35
<211> 540
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(540)
<223> n = A,T,C or G

```

```

<400> 35

```

atagatggaa	tttattaagc	ttttcacatg	tgatagcaca	tagttttaat	tgcacccaaa	60
gtactaacia	aaactctagc	aatcaagaat	ggcagcatgt	tattttataa	caatcaacac	120
ctgtggcctt	taaaatttgg	ttttcataag	ataatttata	ctgaagtaaa	tctagccatg	180
cttttaaaaa	atgcttttagg	tcaactccaag	cttggcagtt	aacatttggc	ataaacaata	240
ataaaacaat	cacaatttaa	taaataacia	atacaacatt	gtaggccata	atcatataca	300
gtataagggg	aaaggtggta	gtgttganta	agcagttatt	agaatagaat	accttggcct	360
ctatgcaaat	atgtctagac	actttgatcc	actcagccct	gacattcagt	tttcaaagtt	420
aggaaacagg	ttctacagta	tcattttaca	gtttccaaca	cattgaaaac	aagtagaaaa	480
tgatganttg	atttttatta	atgcattaca	tcctcaagan	ttatcaccaa	cccctcaggt	540

<210> 36

<211> 555

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(555)

<223> n = A,T,C or G

<400> 36

cttcgtgtgc	ttgaaaattg	gagcctgccc	ctcggcccat	aagcccttgt	tgggaactga	60
gaagtgtata	tggggcccaa	nctactggtg	ccagaacaca	gagacagcag	cccantgcaa	120
tgctgtcgag	cattgcaaac	gccatgtgtg	gaactaggag	gaggaatatt	ccatcttggc	180
agaaaccaca	gcattgggtt	ttttctactt	gtgtgtctgg	gggaatgaac	gcacagatct	240
gtttgacttt	gttataaaaa	tagggctccc	ccacctcccc	cntttctgtg	tnctttattg	300
tagcantgct	gtctgcaagg	gagcccctan	cccctggcag	acanantgc	ttcagtcccc	360
ctttcctctc	tgctaaatgg	atgttgatgc	actggagggtc	ttttancctg	cccttgcattg	420
gcncctgctg	gaggaagana	aaactctgct	ggcatgaccc	acagtttctt	gactggangc	480
cntcaaccct	cttgggtgaa	gccttggtct	gacctgaca	tntgcttggg	cnctgggtng	540
gnctgggctt	ctnaa					555

<210> 37

<211> 280

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(280)

<223> n = A,T,C or G

<400> 37

ccaccgacta	taagaactat	gcctctgtgt	attcctgtac	ctgcatcatc	caactttttc	60
acgtggattt	tgcttggtac	ttggcaagaa	accctaattc	ccctccagaa	acagtggact	120
ctctaaaaaa	tatcctgact	tctaataaca	ttgatntcaa	gaaaatgacg	gtcacagacc	180
aggatgaactg	cccnagctc	tcgtaaccag	gttctacagg	gaggctgcac	ccactccatg	240
ttnccttctgc	ttcgttttcc	cctacccccc	ccccgcctat			280

<210> 38

<211> 303

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 38
catcgagctg gttgtcttct tgctgacct gtgtcgtaaa atgggggtcc cttactgcat 60
tatcaagggg aaggcaagac tgggacgtct agtccacagg aagacctgca ccactgtcgc 120
cttcacacag gtgaactcgg aagacaaagg cgctttggct nagctggtgn aagctatcag 180
gaccaattac aatgacngat acgatnagat ccgccntcac tggggtagca atgtcctggg 240
tcctaagtct gtggctcgta tcgccnagct cgaanaggcn aangctaaag aacttgccac 300
taa 303

<210> 39
<211> 300
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 39
gactcagcgg ctgggtgctct tctgtgacac aagcccagca ctccagggtcc caaggcattt 60
atcaaattccc accaagatnt ttggcttttg caccgaattc tgggtttggt tccctnaaag 120
aactcattga tgtaaatnac tnaaagttag gtctgggtac cctttacatg attccccaga 180
cctcanatgg gctaacacgc ttctcttctc cagcagtctt cctntccgtg aagttacctt 240
ccagattggt acatggaact gaanacaaag ggagcctcag ctngatttaa atctggagca 300

<210> 40
<211> 318
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(318)
<223> n = A,T,C or G

<400> 40
cccaacacaa tggctgagga caaatcagtt ctctgtgacc agacatgaga aggttgccaa 60
tgggctgttg ggcgaccaag gccttcccgg agtcttcgtc ctctatgagc tctcgcccat 120
gatggtgaag ctgacggaga agcacaggtc cttcacccac ttcttgacag gtgtgtgcgc 180
catcattggg ggcatgttca cagtggctgg actcatcgat tcgctcatct accactcagc 240
acgagccatc cagaaaaaaaa ttgatctngg gaagacnacg tagtcaccct cggtncttcc 300
tctgtctcct ctttctcc 318

<210> 41
<211> 302
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(302)

<223> n = A,T,C or G

<400> 41

acttagatgg	ggtccgttca	ggggatacca	gcgttcacat	ttttcctttt	aagaaaggg	60
cttggcctga	atgttcccca	tccggacaca	ggctgcatgt	ctctgttagn	gtcaaagctg	120
ccatnaccat	ctcggtaacc	tactcttact	ccacaatgtc	tatnttcact	gcagggctct	180
ataatnagtc	cataatgtaa	atgcctggcc	caagaentat	ggcctgagtt	tatccnaggc	240
ccaaacnatt	accagacatt	cctcttanat	tgaaaacgga	tntctttccc	ttggcaaaga	300
tc						302

<210> 42

<211> 299

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(299)

<223> n = A,T,C or G

<400> 42

cttaataagt	ttaaggccaa	ggcccgttcc	attcttctag	caactgacgt	tgccagccga	60
ggtttggaca	tacctcatgt	aaatgtggtt	gtcaactttg	acattcctac	ccattccaag	120
gattacatcc	atcgagtagg	tcgaacagct	agagctgggc	gtcccggaaa	ggctattact	180
tttgtcacac	agtatgatgt	ggaactcttc	cagcgcatag	aacacttnat	tgggaagaaa	240
ctaccaggtt	ttccaacaca	ggatgatgag	gttatgatgc	tnacggaacg	cgtcgctna	299

<210> 43

<211> 305

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(305)

<223> n = A,T,C or G

<400> 43

ccaacaatgt	caagacagcc	gtctgtgaca	tcccacctcg	tggcctcaan	atggcagtc	60
ccttcattgg	caatagcaca	gcentccggg	agctcttcaa	gcgcattctc	gagcagttca	120
ctgccatgtt	cgcgcggaag	gccttcctcc	actggtacac	aggcgagggc	atggacaaga	180
tggagttcac	cgaggctgag	agcaacatga	acgacctcgt	ctctnagtat	cagcagtacc	240
gggatgccac	cgcagaaana	ggaggaggat	ttcggttagn	aggccgaaga	aggaggcctg	300
aggca						305

<210> 44

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(399)

<223> n = A,T,C or G

```

<400> 44
tttctgtggg ggaaacctga tctcgacnaa attagagaat tttgtcagcg gtatttcggc      60
tggaacagaa cgaaaaacnga tnaatctctg tttcctgtat taaagcaact cgatncccag      120
cagacacagc tccnaattga ttccttcttt ngattagcac aacagggaga aagaanatgc      180
ttaacgtatt aagagccnga gactaaacag agctttgaca tgratgctta ggaaagagaa      240
agaagcagcn gcccgcgnaa ttngaagcng tttctgttgc cntgganaaa gaatttgagc      300
ttctttatta ggccaacgaa aaaccccgaa ananaggcnt tacnatacct tngaaaantc      360
tccngccnna aaaagaaaga agctttcnga ttcttaacc                               399

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```

<210> 45
<211> 440
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

```

```

<400> 45
gcgggagcag aagctaaagc caaagcccaa gagagtggca gtgccagcac tggtgccagt      60
accagtacca ataacagtgc cagtgccagt gccagcacca gtggtggctt cagtgtcgtt      120
gccagcctga ccgccactct cacatttggg ctcttcgctg gccttggtgg agctggtgcc      180
agcaccagtg gcagctctgg tgcctgtggt ttctcctaca agtgagattt taggtatctg      240
ccttggtttc agtggggaca tctggggcct anggggcngg gataaggagc tggatgattc      300
taggaaggcc cangttggag aangatgtgn anagtgtgcc aagacactgc ttttggcatt      360
ttattccttt ctgtttgctg gangtcaatt gacccttnna ntttctctta cttgtgtttt      420
canatatngt taatcctgcc                               440

```

```

<210> 46
<211> 472
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 46
gctctgtaat ttcacathtt aaaccttccc ttgacctcac attcctcttc ggccacctct      60
gtttctctgt tctctttcac agcaaaaact gttcaaaaaga gttgttgatt actttcattt      120
ccactttctc acccccattc tcccctcaat taactctcct tcatcccat gatgccatta      180
tgtggctntt attanagtca ccaaccttat tctccaaaac anaagcaaca aggactttga      240
cttctcagca gcactcagct ctggtncctg aaacaccccc gttacttgct attcctccta      300
cctcataaca atctccttcc cagcctctac tgetgccttc tctgagttct tcccagggtc      360
ctaggtctcag atgtagtgtg gctcaaccct gctacacaaa gnaatctcct gaaagcctgt      420
aaaaatgtcc atnctgtgcc tgtgagtgat ctncangna naataacaaa tt                               472

```

```

<210> 47
<211> 550
<212> DNA
<213> Homo sapien

```

```

<220>

```

<221> misc_feature

<222> (1)...(550)

<223> n = A,T,C or G

<400> 47

```
ccttcctccg cctggccatc cccagcatgc tcatgctgtg catggagtgg tgggcctatg      60
aggtcgggag cttcctcagt ggtctgtatg aggatggatg acggggactg gtgggaacct      120
gggggcccctg tctgggtgca aggcgacagc tgtctttctt caccaggcat cctcggcatg      180
gtggagctgg gcgctcagtc catcgtgtat gaactggcca tcattgtgta catggtccct      240
gcaggcttca gtgtggctgc cagtgtccgg gtangaaacg ctctgggtgc tggagacatg      300
gaagcaggca cggaagtcct ctaccgtttc cctgctgatt acagtgtctt ttgctgtanc      360
cttcagtgtc ctgctgttaa gctgtaagga tcacntgggg tacattttta ctaccgaccg      420
agaacatcat taatctggtg gctcagggtg ttccaattta tgctgtttcc cacctctttg      480
aagctcttgc tgctcaggta cagcccaatt ttgaaaagta aacaacgtgc ctcggagtgg      540
gaattctgct
```

<210> 48

<211> 214

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(214)

<223> n = A,T,C or G

<400> 48

```
agaaggacat aaacaagctg aacctgccca agacgtgtga tatcagcttc tcagatccag      60
acaacctcct caacttcaag ctggtcattt gtcttgatna gggcttctac nagagtggga      120
agtttgtgtt cagttttaag gtggggccagg gttaccgcga tgatccccc aaggtgaagt      180
gtgagacnat ggtctatcac cccnacattg acct
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<210> 49

<211> 267

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(267)

<223> n = A,T,C or G

<400> 49

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atctgcctaa aatttattca aataatgaaa atnaatctgt tttaagaaat tcagtctttt      60
agtttttagg acaactatgc acaaatgtac gatggagaat tctttttgga tnaactctag      120
gtngaggaac ttaatccaac cggagctntt gtgaagggtc gaanacagga gaggggaatct      180
tggcaaggaa tggagacnga gtttgcaaat tgcagctaga gtnaatngtt ntaaattggga      240
ctgctnttgt gtctcccgaa gaaagtt
```

<210> 50

<211> 300

<212> DNA

<213> Homo sapien

<220>

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<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 50
gactgggtca aagctgcatg aaaccaggcc ctggcagcaa cctgggaatg gctggaggtg      60
ggagagaacc tgacttctct tccctctcc ctcctccaac attactggaa ctctgtcctg      120
ttgggatctt ctgagcttgt tccctgctg ggtgggacag aggacaaagg agaagggagg      180
gtctagaaga ggcagccctt ctttgtctc tggggtnaat gagcttgacc tanagtagat      240
ggagagacca anagcctctg atttttaatt tccataanat gttcnaagta tatntntacc      300

<210> 51
<211> 300
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 51
gggtaaaatc ctgcagcacc cactctggaa aatactgctc ttaattttcc tgaagggtgg      60
cccctatttc tagttggtcc aggattaggg atgtggggta tagggcattt aaatcctctc      120
aagcgtcttc caagcacccc cggcctgggg gtnagtttct catcccgtca ctgctgctgg      180
gatcaggttn aataaatgga actcttctg tctggcctcc aaagcagcct aaaaactgag      240
gggctctgtt agagggggacc tccaccctnn ggaagtccga ggggctnggg aagggtttct      300

<210> 52
<211> 267
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

<400> 52
aaaatcaact tcntgcatta atanacanat tctanancag gaagtgaana taattttctg      60
cacctatcaa ggaacnnact tgattgcctc tattnaacan atatatcgag ttncataact      120
tacctgaata ccnccgcata actctcaacc nanatncntc nccatgacac tcnttcttna      180
atgctantcc cgaattcttc attatatcng tgatgttcgn cctgntnata tatcagcaag      240
gtatgtncnn taactgccga nncaang                                     267

<210> 53
<211> 401
<212> DNA
<213> Homo sapien

<400> 53
agscctttagc atcatgtaga agcaaactgc acctatggct gagataggtg caatgacctg      60
caagatcttg tgctttctag ctgtccagga aaagccatct tcagtcttgc tgacagtcaa      120
agagcaagtg aaaccatttc cagcctaaac tacataaaag cagccgaacc aatgattaaa      180
gacctctaag gctccataat catcattaaa tatgcccaaa ctcattgtga ctttttattt      240
```

tatatacagg	attaaaaatca	acattaaatc	atcttattta	catggccatc	ggtgctgaaa	300
ttgagcattt	taaatagtac	agtaggctgg	tatacattag	gaaatggact	gcactggagg	360
caaatagaaa	actaaagaaa	ttagataggc	tggaaatgct	t		401

<210> 54
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 54						
cccaacacaa	tggataaaaa	cacttatagt	aaatggggac	attcactata	atgatctaag	60
aagctacaga	ttgtcatagt	tgttttcctg	ctttacaaaa	ttgctccaga	tctggaatgc	120
cagtttgacc	tttgtcttct	ataatatttc	ctttttttcc	cctctttgaa	tctctgtata	180
tttgattctt	aactaaaatt	gttctcttaa	atattctgaa	tcctggtaat	taaaagtttg	240
ggtgtatttt	ctttacctcc	aaggaaagaa	ctactagcta	caaaaaatat	tttggaataa	300
gcattgtttt	ggtataaggt	acatattttg	gttgaagaca	ccagactgaa	gtaaacagct	360
gtgcatccaa	tttattatag	ttttgtaagt	aacaatatgt	a		401

<210> 55
 <211> 933
 <212> DNA
 <213> Homo sapien

<400> 55						
tttactgctt	ggcaaagtac	cctgagcatc	agcagagatg	ccgagatgaa	atcagggaac	60
tcctagggga	tgggtcttct	attacctggg	aacacctgag	ccagatgcct	tacaccacga	120
tgtgcatcaa	ggaatgcctc	cgctctacg	caccggtagt	aaactatccc	ggttactcga	180
caaaccctac	acctttccag	atggacgctc	cttacctgca	ggaataactg	tgtttatcaa	240
tatttgggct	cttcaccaca	acctctat	ctgggaagac	cctcaggtct	ttaaccctt	300
gagattctcc	agggaaaatt	ctgaaaaaat	acatccctat	gccttcatac	cattctcagc	360
tggattaagg	aactgcattg	ggcagcattt	tgccataatt	gagtgtaaag	tggcagtggt	420
attaactctg	ctccgcttca	agctggctcc	agaccactca	aggccaccca	gctgtcgtca	480
agttgectca	agtccaagaa	tggaatccat	gtgtttgcaa	aaaaagtttg	ctaattttaa	540
gtccttttctg	tataagaatt	aakgagacaa	tttctctacc	aaaggaagaa	caaaaggata	600
aatataatac	aaaatatatg	tatatggttg	tttgacaaat	tatataactt	aggatacttc	660
tgactgggtt	tgacatccat	taacagtaat	tttaatttct	ttgctgtatc	tgggtgaaacc	720
cacaaaaaca	cctgaaaaaa	ctcaagctga	gttccaatgc	gaagggaaat	gattggtttg	780
ggtaactagt	ggtagagtgg	ctttcaagca	tagtttgatc	aaaactccac	tcagtatctg	840
cattactttt	atctctgcaa	atatctgcat	gatagcttta	ttctcagtta	tctttcccca	900
taataaaaaa	tatctgccaa	aaaaaaaaaa	aaa			933

<210> 56
 <211> 480
 <212> DNA
 <213> Homo sapien

<400> 56						
ggctttgaag	catttttgtc	tgtgctccct	gatcttcagg	tcaccaccat	gaagttctta	60
gcagtctctg	tactcttggg	agtttccatc	tttctgggtc	ctgcccagaa	tccgacaaca	120
gctgctccag	ctgacacgta	tccagctact	ggtcctgctg	atgatgaagc	ccctgatgct	180
gaaaccactg	ctgctgcaac	cactgcgacc	actgctgctc	ctaccactgc	aaccaccgct	240
gcttctacca	ctgctcgtaa	agacattcca	gttttaccca	aatgggttgg	ggatctcccg	300
aatggtagag	tgtgtccctg	agatggaatc	agcttgagtc	ttctgcaatt	ggtcacaact	360
attcatgctt	cctgtgattt	catccaacta	cttaccttgc	ctacgatatc	ccctttatct	420
ctaatacagt	tattttcttt	caaataaaaa	ataactatga	gcaacaaaaa	aaaaaaaaaa	480

<210> 57
 <211> 798
 <212> DNA
 <213> Homo sapien

<400> 57
 agcctacctg gaaagccaac cagtcctcat aatggacaag atccaccagc tcctcctgtg 60
 gactaacttt gtgatatggg aagtgaaaat agttaacacc ttgcacgacc aaacgaacga 120
 agatgaccag agtactctta accccttaga actgtttttc cttttgtatc tgcaatatgg 180
 gatggatttg ttttcatgag cttctagaaa ttccacttgc aagtttattt ttgcttcctg 240
 tgttactgcc attcctatct acagtatatt tgagtgaatg attatatttt taaaaagtta 300
 catgggggctt ttttggttgt cctaaactta caaacattcc actcattctg tttgtaactg 360
 tgattataat ttttgtgata atttctggcc tgattgaagg aaatttgaga ggtctgcatt 420
 tatatatctt aaatagattt gataggtttt taaattgctt tttttcataa ggtatttata 480
 aagttatttg gggttgtctg ggattgtgtg aaagaaaatt agaaccctgc tgtatttaca 540
 tttaccttgg tagtttattt gtggatggca gttttctgta gttttgggga ctgtggtagc 600
 tcttggattg ttttgcaaat tacagctgaa atctgtgtca tggattaaac tggcttatgt 660
 ggctagaata ggaagagaga aaaaatgaaa tggttgttta ctaattttat actcccatta 720
 aaaattttta atgttaagaa aaccttaaat aaacatgatt gatcaatatg gaaaaaaaaa 780
 aaaaaaaaaa aaaaaaaaaa 798

<210> 58
 <211> 280
 <212> DNA
 <213> Homo sapien

<400> 58
 ggggcagctc ctgaccctcc acagccacct ggtcagccac cagctggggc aacgaggggtg 60
 gaggtccac tgagcctctc gcctgcccc gccactcgtc tgggtgcttg tgatccaagt 120
 ccctgcctg gtccccaca aggactccca tccaggcccc ctctgccctg ccccttgctca 180
 tggaccatgg tctgaggaa gggctcatgc cccttattta tgggaaccat ttcattctaa 240
 cagaataaac cgagaaggaa accagaaaaa aaaaaaaaaa 280

<210> 59
 <211> 382
 <212> DNA
 <213> Homo sapien

<400> 59
 aggcgggagc agaagctaaa gccaaagccc aagagagtgg cagtgccagc actggtgcca 60
 gtaccagtac caataacagt gccagtcca gtgccagcac cagtgggtggc ttcagtgtctg 120
 gtgccagcct gaccgccact ctcacatttg ggtctctcgc tggccttggg ggagctggtg 180
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat ttagatatt 240
 gtaaatcctg ccagtccttc tcttcaagcc aggggtgcac ctcagaaacc tactcaacac 300
 agcactctag gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg 360
 ccattaaaaa aaaaaaaaaa aa 382

<210> 60
 <211> 602
 <212> DNA
 <213> Homo sapien

<400> 60
 tgaagagccg cgcggtggag ctgctgccc atgggactgc caaccttgcc aagctgcagc 60

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ttgtggtgga gaatagtgcc cagcgggtca tccacttggc gggtcagtgg gagaagcacc 120
gggtcccatc ctctgtgagta ccgccactcc gaaagctgca ggattgcaga gagctggaat 180
cttctcgacg gctggcagag atccaagaac tgcaccagag tgtccggcg gctgctgaag 240
aggcccgag gaaggaggag gtctataagc agctgatgtc agagctggag actctgcca 300
gagatgtgtc ccggtggcc tacacccagc gcacccctgga gatcgtggc aacatccgga 360
agcagaagga agagatcacc aagatcttgt ctgatacga ggagcttcag aaggaaatca 420
actccctatc tgggaagctg gaccggacgt ttgctgtgac tgatgagctt gtgttcaagg 480
atgccaagaa ggacgatgct gttcggagg cctataagta tctagctgct ctgcacgaga 540
actgcagcca gctcatccag accatcgagg acacaggcac catcatgcgg gaggttcgag 600
ac 602

```

```

<210> 61
<211> 1368
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(1368)
<223> n = A,T,C or G

```

```

<400> 61
ccagtgagcg cgcgtaatac gactcactat agggcgaatt gggtagcggg cccccctcg 60
agcggccgcc cttttttttt tttttttatt gatcagaatt caggctttat tattgagcaa 120
tgaaaacagc taaaacttaa ttccaagcat gtgtagttaa agtttgcaa gtgggatatt 180
gttcacaaaa cacattcaat gtttaaacac tatttatttg aagaacaaaa tatatttaaa 240
attgtttgct tctaaaaagc ccatttccct ccaagtctaa actttgtaat ttgatattaa 300
gcaatgaagt tattttgtac aatctagtta aacaagcaga atagcactag gcagaataaa 360
aaattgcaca gacgtatgca atttccaag atagcattct ttaaattcag ttttcagctt 420
ccaaagattg gttgcccata atagacttaa acatataatg atggctaaaa aaaataagta 480
tacgaaaatg taaaaaagga aatgtaagtc cactctcaat ctcataaaa gtgagagtaa 540
ggatgctaaa gcaaaaataaa tgtaggttct ttttttctgt ttccgtttat catgcaatct 600
gcttctttga tatgccttag ggttacccat ttaagttaga gggttgtaat caatggtggg 660
aatgaaaatt gatcaaatat acaccttgc atttcatttc aaattgcggg ctggaaactt 720
ccaaaaaaag ggtaggcagc aagaaaaaaa aaatcmaatc agaacctctt caggggtttg 780
kgktctgata tggcagacar gatacaagtc ccaccaggag atggagcaat tcaaaataag 840
ggtaattggc tgacaaggtg ttattgccag catgggacag aatgagcaac aggcgaaaa 900
gtttttggat tatatagcac ctatagcttc tgatgtaggg aatttttgtt agtcaaacat 960
acgctaaact tccaaggga aatctttcag gtagecctaag cttgcttttc tagagtgatg 1020
agttgcattg ctactgtgat tttttgaaaa caaactgggt ttgtacaagt gagaaagact 1080
agagagaaaag attttagtct gtttagcaga agccatttta tctgcgtgca catggatcaa 1140
tattttctgat cccctatacc ccaggaaggc caaaatccca aagaaatgtg ttagcaaaat 1200
tggtctgatc tatcatattg ctatggacat tgatcttgcc caacacaatg gaattccacc 1260
acactggact agtggatcca ctatgtctag agcggccggc caccgcggtg gagctccagc 1320
ttttgttccc tttagtgagg gtttaattgcg cgcttggcgt aatcatnn 1368

```

```

<210> 62
<211> 924
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(924)
<223> n = A,T,C or G

```

<400> 62

caaaggnaca	ggaacagctt	gnaaagtact	gncatncctn	cctgcaggga	ccagcccttt	60
gcctccaaaa	gcaataggaa	attttaaaga	tttncactga	gaaggggncc	acgttttnart	120
tntnaatgt	tcargnanar	tnccttncaa	atgncrnctn	cactnactnr	gnatttgggt	180
tnccgnrtnc	mgnactatnt	caggtttgaa	aaactggatc	tgccacttat	cagttatgtg	240
accttaaaga	actccgttaa	tttctcagag	cctcagtttc	cttgtctata	agttgggagt	300
aatattaata	ctatcatttt	tccaaggatt	gatgtgaaca	ttaatgaggt	gaaatgacag	360
atgtgtatca	tggttcctaa	taaacatcca	aaatatagta	cttactattg	tcattattat	420
tacttgtttg	aagctaaaga	cctcacataa	gaatcccatc	cagcccacca	gacagagyt	480
tgagttttct	agtttggaag	agctattaaa	taacaacktc	tagtgtcaat	tctatacttg	540
ttatgggtcaa	gtaactgggc	tcagcatttt	acattcattg	tctctttaag	ttctagcaat	600
gtgaagcagg	aactatgatt	atattgacta	cataaatgaa	gaaattgagg	ctcagatata	660
ttaagtaatt	ctcccagggt	cacacagcta	gaactggcaa	agcctgggat	tgatccatga	720
tcttccagca	ttgaagaatc	ataaatgtaa	ataactgcaa	ggccttttcc	tcagaagagc	780
tctgtgtgt	tgcaccaacc	cactagcact	tgttctctac	aggggaacat	ctgtgggcct	840
gggaatcact	gcacgtcgca	agagatgttg	cttctgatga	attattgttc	ctgtcagtgg	900
tgtgaaggca	aaaaaaaaaa	aaaa				924

<210> 63

<211> 1079

<212> DNA

<213> Homo sapien

<400> 63

agtcccaaga	actcaataat	ctcttatgtt	ttcttttgaa	gacttatttt	aaatattaac	60
tatttcggtg	cctgaatgga	aaaatataaa	cattagctca	gagacaatgg	ggtacctgtt	120
tggaaatccag	ctggcagcta	taagcaccgt	tgaaaactct	gacaggcttt	gtgccctttt	180
tattaaatgg	cctcacatcc	tgaatgcagg	aatgtgttcg	tttaaataaa	cattaatcct	240
taatgttgaa	ttctgaaaac	acaaccataa	atcatagttg	gtttttctgt	gacaatgatc	300
tagtacatta	tttctctcac	agcaaaccta	cctttccaga	aggtggaaat	tgtatttgca	360
acaatcaggg	caaaaccac	acttgaaaag	cattttacaa	tattatatct	aagttgcaca	420
gaagacccca	gtgatcacta	ggaaatctac	cacagtcag	tttttcta	ccaagaagg	480
caaacttcgg	ggaataatgt	gtccctcttc	tgtgtgtgt	ctgaaaaata	ttcgatcaaa	540
acgaagttaa	taagcagcag	ttattccaag	attagagttc	atttgtgtat	cccatgtata	600
ctggcaatgt	ttaggtttgc	ccaaaaactc	ccagacatcc	acaatgttgt	tgggtaaacc	660
accacatctg	gtaacctctc	gatcccttag	atttgtatct	cctgcaata	taactgtagc	720
tgactctgga	gcctcttgca	ttttctttaa	aaccattttt	aactgattca	ttcgttccgc	780
agcatgccct	ctggtgctct	ccaaatggga	tgtcataagg	caaagctcat	ttcctgacac	840
attcacatgc	acacataaaa	ggtttctcat	cattttggta	cttggaaaag	gaataatctc	900
ttgggttttt	aatttcactc	ttgatttctt	caacattata	gctgtgaaat	atccttcttc	960
atgacctgta	ataatctcat	aattacttga	tctcttcttt	aggtagctat	aatatggggg	1020
aataacttcc	tgtagaaata	tcacatctgg	gctgtacaaa	gctaagtagg	aacacaccc	1079

<210> 64

<211> 1001

<212> DNA

<213> Homo sapien

<400> 64

gaatgtgcaa	cgatcaagtc	agggatatctg	tggatccac	cactttgagc	atttatcgat	60
tctatatgtc	aggaacattt	caagttatct	gttctagcaa	ggaaatataa	aatacttata	120
gttaactatg	gcctatctac	agtgcacta	aaaactagat	tttattcctt	tccacctgtg	180
ggtttgatt	catttaccac	cctcttttca	ttccctttct	cacccacaca	ctgtgccggg	240
cctcaggcat	atactattct	actgtctgtc	tctgtaagga	ttatcatttt	agcttccaca	300

tatgagagaa	tgcattgcaaa	gtttttcttt	ccatgtctgg	cttatttcac	ttaacataat	360
gacctcgct	tccatccatg	ttatttatat	tacccaatag	tggtcataaa	tatatataca	420
cacatatata	ccacattgca	tttgtccaat	tattcattga	cggaaactgg	ttaatgttat	480
atcggtgcta	ttgtggatag	tgctgcaata	aacacgcaag	tggggatata	atttgaagag	540
tttttttggt	gatgttcctc	caaattttta	gattgttttg	tctatgtttg	tgaaaaaggc	600
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tctacatttt	ctttcatcaa	agttttgttg	tatttttgaa	gtagatgtat	ttcaccttat	780
agatcaagtg	tattccctaa	atattttatt	tttgtagcta	ttgtagatga	aattgccttc	840
ttgatttctt	tttcacttaa	ttcattatta	gtgtatggaa	atgttatgga	tttttatttg	900
ttggttttta	atcaaaaact	gtattaaact	tagagttttt	tgtggagttt	ttaagttttt	960
ctagatataa	gatcatgaca	tctacccaaa	aaaaaaaaaa	a		1001

<210> 65

<211> 575

<212> DNA

<213> Homo sapien

<400> 65

acttgatata	aaaaggatat	ccataatgaa	tattttatac	tgcattcctt	acattagcca	60
ctaaatacgt	tattgcttga	tgaagacctt	tcacagaatc	ctatggattg	cagcatttca	120
cttggtact	tcatacccat	gccttaaaga	ggggcagttt	ctcaaaagca	gaaacatgcc	180
gccagttctc	aagttttcct	cctaactcca	tttgaatgta	agggcagctg	gccccaatg	240
tggggaggtc	cgaacatttt	ctgaattccc	attttcttgt	tcgcggctaa	atgacagt	300
ctgtcattac	ttagattccc	gatctttccc	aaagggtgtg	atttacaag	aggccagcta	360
atagccagaa	atcatgacct	tgaagagag	atgaaatttc	aagctgtgag	ccaggcagga	420
gctccagtat	ggcaaagggt	cttgagaatc	agccatttgg	tacaaaaaag	atttttaag	480
cttttatgtt	ataccatgga	gccatagaaa	ggctatggat	tgtttaagaa	ctattttaaa	540
gtgttccaga	cccaaaaagg	aaaaaaaaaa	aaaaa			575

<210> 66

<211> 831

<212> DNA

<213> Homo sapien

<400> 66

attgggctcc	ttctgctaaa	cagccacatt	gaaatggttt	aaaagcaagt	cagatcaggt	60
gatttgtaaa	attgtattta	tctgtacatg	tatgggcttt	taattcccac	caagaaagag	120
agaaattatc	tttttagtta	aaaccaaatt	tcacttttca	aaatatcttc	caacttattt	180
attggttgtc	actcaattgc	ctatatatat	atatatatat	gtgtgtgtgt	gtgtgtgcgc	240
gtgagcgcac	gtgtgtgtat	gcgtgcgcac	gtgtgtgtat	gtgtattatc	agacataggt	300
ttctaacttt	tagatagaag	aggagcaaca	tctatgccaa	atactgtgca	ttctacaatg	360
gtgctaattc	cagacctaaa	tgatactcca	tttaatttaa	aaaagagttt	taaataatta	420
tctatgtgcc	tgtatttccc	ttttgagtg	tgcacaacat	gttaacatat	tagtgtaaaa	480
gcagatgaaa	caaccacgtg	ttctaaggtc	tagggattgt	gctataatcc	ctatttagtt	540
caaaattaac	cagaattctt	ccatgtgaaa	tggaccaaac	tcatattatt	gttatgtaaa	600
tacagagttt	taatgcagta	tgacatccca	caggggaaaa	gaatgtctgt	agtgggtgac	660
tgttatcaaa	tattttatag	aatacaatga	acggtgaaca	gactggtaac	ttgtttgagt	720
tcccatgaca	gatttgagac	ttgtcaatag	caaatcattt	ttgtatttaa	atttttgtac	780
tgatttgaaa	aacatcatta	aatatcttta	aaagtaaaaa	aaaaaaaaaa	a	831

<210> 67

<211> 590

<212> DNA

<213> Homo sapien

<400> 67
 gtgctctgtg tattttttta ctgcattaga cattgaatag taatttgcgt taagatacgc 60
 ttaaaggctc tttgtgacca tgtttccctt tgtagcaata aaatgtttt tacgaaaact 120
 ttctccctgg attagcagtt taaatgaaac agagtccatc aatgaaatga gtatttataa 180
 taaaaatttg ccttaaatgta tcagttcagc tcacaagtat tttaaatga ttgagaagac 240
 ttgaattaaa gaaaaaaaaa ttctcaatca tattttttaa atataagact aaaattgttt 300
 ttaaaacaca tttcaaatag aagtggagtt gaactgacct tatttatact ctttttaagt 360
 ttgttccttt tccctgtgcc tgtgtcaaat cttcaagtct tgctgaaaat acatttgata 420
 caaagttttc tgtagttgtg ttagttcttt tgtcatgtct gtttttggct gaagaaccaa 480
 gaagcagact tttcttttaa aagaattatt tctctttcaa atatttctat ccttttttaa 540
 aaattccctt ttatggctta tatacctaca tatttataaa aaaaaaaaaa 590

<210> 68
 <211> 291
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (291)
 <223> n = A,T,C or G

<400> 68
 gttccctttt ccggctcggcg tggctcttgcg agtggagtg cgcgtgtgcc cgggcctgca 60
 ccatgagcgt ccggccttc atcgacatca gtgaagaaga tcaggctgct gagcttcgtg 120
 cttatctgaa atctaaagga gctgagattt cagaagagaa ctcggaaggt ggacttcatg 180
 ttgatttagc tcaaatattt gaagcctgtg atgtgtgtct gaaggaggat gataaagatg 240
 ttgaaagtgt gatgaacagt ggggnatcct actcttgatc cggaanccna c 291

<210> 69
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (301)
 <223> n = A,T,C or G

<400> 69
 tctatgagca tgccaaggct ctgtgggagg atgaaggagt gcgtgcctgc tacgaacgct 60
 ccaacgagta ccagctgatt gactgtgccc agtacttcct ggacaagatc gacgtgatca 120
 agcaggctga ctatgtgccg agcgatcagg acctgcttcg ctgccgtgtc ctgacttctg 180
 gaatctttga gaccaagttc caggtggacn aagtcaactt ccacatgntt gacgtgggtg 240
 gccagcgcga tgaacgccgc aagtggatcc agtgcttcaa cgatgtgact gccatcatct 300
 t 301

<210> 70
 <211> 201
 <212> DNA
 <213> Homo sapien

<400> 70
 gcggctcttc ctcgggcagc ggaagcggcg cggcggtcgg agaagtggcc taaaacttcg 60

```
gcgttgggtg aaagaaaatg gcccgaacca agcagactgc tcgtaagtcc accggtggga 120
aagccccccg caaacagctg gccacgaaag ccgccaggaa aagcgctccc tctaccggcg 180
gggtgaagaa gcctcatcgc t 201
```

```
<210> 71
<211> 301
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G
```

```
<400> 71
gccggggtag tcgccgnccg cgccgccgct gcagccactg caggcacccg tgcgcgcccc 60
tgagtagtgg gcttaggaag gaagaggtca tctcgctcgg agcttcgctc ggaagggtct 120
ttgttccttg cagccctccc acgggaatga caatggataa aagtgaactg gtacanaaag 180
ccaaactcgc tgagcaggct gagcgatatg atgatatggc tgcagccatg aaggcagtca 240
cagaacaggg gcatgaactc ttcaacgaag agagaaatct gctctctggt gcctacaaga 300
a 301
```

```
<210> 72
<211> 251
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(251)
<223> n = A,T,C or G
```

```
<400> 72
cttggggggg gttggggggg agactgtggg cctggaaata aaacttgtct cctctaccac 60
caccctgtac cctagcctgc acctgtccac atctctgcaa agttcagctt ccttccccag 120
gtctctgtgc actctgtctt ggatgctctg gggagctcat gggaggagga gtctccacca 180
gagggaggct caggggactg gttggggccag ggatgaatat ttgagggata aaaatttgtt 240
aagagccaan g 251
```

```
<210> 73
<211> 895
<212> DNA
<213> Homo sapien
```

```
<400> 73
tttttttttt tttttcccag gccctctttt tatttacagt gataccaaac catccacttg 60
caaattcttt ggtctcccat cagctggaat taagtaggta ctgtgtatct ttgagatcat 120
gtatttgtct ccactttggg ggatacaaga aaggaaggca cgaacagctg aaaaagaagg 180
gtatcacacc gctccagctg gaatccagca ggaacctctg agcatgccac agctgaacac 240
ttaaagagg aaagaaggac agctgctctt catttatttt gaaagcaaat tcatttgaaa 300
gtgcataaat ggtcatcata agtcaaacgt atcaattaga ccttcaacct aggaaacaaa 360
attttttttt tctatttaat aatacaccac actgaaatta tttgccaatg aatcccaaag 420
atttggtaca aatagtacaa ttcgtatttg ctttctcttt tcctttcttc agacaaacac 480
caaataaaat gcagggtgaaa gagatgaacc acgactagag gctgacttag aaatttatgc 540
tgactcgatc taataaaaaat tatgttggtt aatgttaatc tatctaaaat agagcatttt 600
```

gggaatgctt	ttcaaagaag	gtcaagtaac	agtcatacag	ctagaaaagt	ccctgaaaaa	660
aagaattggt	aagaagtata	ataacctttt	caaaacccac	aatgcagctt	agttttcctt	720
tattttattg	tggcatgaa	gactatcccc	atttctccat	aaaatcctcc	ctccatactg	780
ctgcattatg	gcacaaaaga	ctctaagtgc	caccagacag	aaggaccaga	gtttctgatt	840
ataaacaatg	atgctgggta	atgtttaaat	gagaacattg	gatatggatg	gtcag	895

<210> 74
 <211> 351
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(351)
 <223> n = A,T,C or G

<400> 74						
tgtgcncagg	ggatgggtgg	gcngtggaga	ngatgacaga	aaggctggaa	ggaanggggg	60
tgggtttgaa	ggccanggcc	aaggggncct	caggtccgnt	tctgnnaagg	gacagccttg	120
aggaaggagn	catggcaagc	catagctagg	ccaccaatca	gattaagaaa	nnctgagaaa	180
nctagctgac	catcactggt	ggtgnccagt	ttcccaacac	aatggaatnc	caccacactg	240
gactagnnga	nccactagtt	ctagagcggc	cgccaccgcg	gtggaacccc	aacttttgcc	300
cctttagnga	gggttaattg	cgcgcttggc	ntaatcatgg	tcataagctg	t	351

<210> 75
 <211> 251
 <212> DNA
 <213> Homo sapien

<400> 75						
tacttgacct	tctttgaaaa	gcattcccaa	aatgctctat	tttagataga	ttaacattaa	60
ccaacataat	tttttttaga	tcgagtcagc	ataaatttct	aagtcagcct	ctagtcgtgg	120
ttcatctctt	tcacctgcat	tttatttggt	gtttgtctga	agaaaggaaa	gaggaaagca	180
aatacgaatt	gtactatttg	taccaaactc	ttgggattca	ttggcaaata	atttcagtgt	240
ggtgtattat	t					251

<210> 76
 <211> 251
 <212> DNA
 <213> Homo sapien

<400> 76						
tattttaataa	tacaccacac	tgaaattatt	tgccaatgaa	tcccaaagat	ttggtacaaa	60
tagtacaatt	cgtatttgct	ttcctctttc	ctttcttcag	acaaacacca	aataaaatgc	120
aggtgaaaga	gatgaaccac	gactagaggc	tgacttagaa	atttatgctg	actcgatcta	180
aaaaaaatta	tgttgggttaa	tgtaaatcta	tctaaaatag	agcatttttg	gaatgctttt	240
caaagaaggt	c					251

<210> 77
 <211> 351
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

<222> (1)...(351)

<223> n = A,T,C or G

<400> 77

actcaccgtg	ctgtgtgctg	tgtgcctgct	gcctggcagc	ctggccctgc	cgtgctcag	60
gagggcgagg	gcatgagtga	gctacagtgg	gaacaggctc	aggactatct	caagagannn	120
tatctctatg	actcagaaac	aaaaaatgcc	aacagtttag	aagccaaact	caaggagatg	180
caaaaattct	ttggcctacc	tataactgga	atgttaaact	cccgcgtcat	agaaataatg	240
cagaagccca	gatgtggagt	gccagatggt	gcagaatact	cactatttcc	aaatagccca	300
aaatggactt	ccaaagtggg	cacctacagg	atcgtatcat	atactcgaga	c	351

<210> 78

<211> 1574

<212> DNA

<213> Homo sapien

<400> 78

gccctggggg	cggaggggag	gggcccacca	cggccttatt	tccgcgagcg	ccggcactgc	60
ccgtccgag	cccgtgtctg	tcgggtgccg	agccaacttt	cctgcgtcca	tgcagccccg	120
ccggcaacgg	ctgcccgtc	cctgggtccg	gcccaggggc	ccgcgcccc	ccgccccgct	180
gctcgcgtg	ctgtgttgc	tcgccccgg	ggcgcgccc	gcgggggtccg	gggaccccg	240
cgacctggg	cagcctcagg	atgctgggg	cccgcgcagg	ctcctgcagc	aggcggcgcg	300
cgcggcgctt	cacttcttca	acttccggc	cggctcgccc	agcgcgctgc	gagtgtggc	360
cgaggtgcag	gagggccgcg	cgtggattaa	tccaaaagag	ggatgtaaag	ttcacgtggg	420
cttcagcaca	gagcgctaca	accagagtc	tttacttcag	gaaggtgagg	gacgtttggg	480
gaaatgttct	gtcgcagtgt	ttttcaagaa	tcagaaaacc	agaccaacta	tcaatgtaac	540
ttgtacacgg	ctcatcgaga	aaaagaaaag	acaacaagag	gattacctgc	tttacaagca	600
aatgaagcaa	ctgaaaaacc	ccttggaat	agtcagcata	cctgataatc	atggacatat	660
tgatccctct	ctgagactca	tctgggattt	ggctttcctt	ggaagctctt	acgtgatgtg	720
ggaaatgaca	acacaggtgt	cacactacta	cttggcacag	ctcactagt	tgaggcagtg	780
gaaaactaat	gatgatacaa	ttgattttga	ttatactgtt	ctacttcatg	aattatcaac	840
acaggaaata	attccctgtc	gcattcactt	ggctctgtac	cctggcaaac	ctcttaaagt	900
gaagtaccac	tgtaagagc	tacagacacc	agaagaagcc	tccggaactg	aagaaggatc	960
agctgtagta	ccaacagagc	ttagtaattt	ctaaaaagaa	aaaatgatct	ttttccgact	1020
tctaaacaag	tgactatact	agcataaatc	attcttctag	taaaacagct	aaggatataga	1080
cattctaata	atttgggaaa	acctatgatt	acaagtaaaa	actcagaaat	gcaaagatgt	1140
tggttttttg	tttctcagtc	tgctttagct	tttaactctg	gaagcgcatg	cacactgaac	1200
tctgctcagt	gctaaacagt	caccagcagg	ttcctcaggg	tttcagccct	aaaatgtaaa	1260
acctggataa	tcagtgtatg	ttgcaccaga	atcagcattt	tttttttaac	tgcaaaaaat	1320
gatgggtctca	tctctgaatt	tatatctctc	attcttttga	acatactata	gctaatatat	1380
tttatgttgc	taaattgctt	ctatctagca	tgttaaacaa	agataatata	ctttcgatga	1440
aagtaaatta	taggaaaaaa	attaactgtt	ttaaaaagaa	cttgattatg	ttttatgatt	1500
tcaggcaagt	attcattttt	aacttgctac	ctacttttaa	ataaatgttt	acattttctaa	1560
aaaaaaaaaa	aaaa					1574

<210> 79

<211> 401

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(401)

<223> n = A,T,C or G

<400> 79
catactgtga attgttcttg actccttttc ttgacattca gttttcanaa tttccatctt 60
tcttctggaa ctaatgtgct gttctcttga ctgcctgctg ggccagcatc cgattgccag 120
ccagaaacgt cacactgccc aagatggcca ggtacttcaa ggtctggaac atgttgagct 180
gagtcagta gacatacatg agtcccagca tagcagcatg tcccagggtga aatataatcg 240
tgctaggagc aaaagtgaag ttggagacat tggcaccaat ccggatccac tagttctaga 300
gcggccgcca ccgcggtgga gctccagctt ttgttccctt tagtgagggg taattgcgcg 360
cttggcgtaa tcatggnat agctgtttcc tgtgtgaaat t 401

<210> 80
<211> 301
<212> DNA
<213> Homo sapien

<400> 80
aaaaatgaaa catctatctt agcagcaaga ggctgtgagg gatggggtag aaaaggcatc 60
ctgagagagt tctagaccga cccaggctct gtggcacact atacgggtca ggaggggtgg 120
aagacaggcc taagctctag gacgggtgaat ctcggggcta tttgtggatt tgttagaaac 180
agacattctt ttggcctttt cctggcactg gtgttgccgg cagggtgggca gaagtgagcc 240
accagtcact gttcagtcac tgccaccaca gatcttcagc agaatcttcc ggtaatcccc 300
t 301

<210> 81
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 81
tagccagggt gctcaagcta attttattct ttcccaacag gatccatttg gaaaatatca 60
agcctttaga atgtggcagc aagagaaagc ggactacgca ggaacgggga gtttgggaga 120
agctctcctg gtgttgactt agggatgaag gctccaggct gctgccagaa atggagtcac 180
cagcagaaga actgntttct ctgataagga tgccccacca ttttcaagct gttcgttaaa 240
gttacacagg tcttctctgc agcagtaagt accgtagct cattttccct caagcggggt 300
t 301

<210> 82
<211> 201
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(201)
<223> n = A,T,C or G

<400> 82
tcaacagaca aaaaaagttt attgaatata aaactcaaag gcatcaacag tcctgggccc 60
aagagatcca tggcaggaag tcaagagttc tgcttcaggg tcggtctggg cagccctgga 120
agaagtcatt gcacatgaca gtgatgagtg ccaggaaaac agcatactcc tggaaagtcc 180
acctgctggg cactgnttca t 201

<210> 83
 <211> 251
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(251)
 <223> n = A,T,C or G

<400> 83
 gtaaggagca tactgtgccc atttattata gaatgcagtt aaaaaaata ttttgagggt 60
 agcctctcca gtttaaaagc acttaacaag aaacacttgg acagcgatgc aatgggtctct 120
 cccaaaccgg ctccctctta ccaagtaccg taaacagggt ttgagaacgt tcaatcaatt 180
 tcttgatatg aacaatcaaa gcattttaatg caaacatatt tgcttctcaa anaataaaac 240
 cattttccaa a 251

<210> 84
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 84
 agttttataat gttttactat gatttagggc ttttttttca aagaacaaaa attataagca 60
 taaaaactca ggtatcagaa agactcaaaa ggctgttttt cactttgttc agattttggt 120
 tccaggcatt aagtgtgtca tacagttgtt gccactgctg ttttccaaat gtccgatgtg 180
 tgctatgact gacaactact tttctctggg tctgatcaat tttgcagtan accatttttag 240
 ttcttacggc gtcnataaca aatgcttcaa catcatcagc tccaatctga agtcttgctg 300
 c 301

<210> 85
 <211> 201
 <212> DNA
 <213> Homo sapien

<400> 85
 tatttggtgta tgtaacattt attgacatct acccactgca agtatagatg aataagacac 60
 agtcacacca taaaggagtt tctccttaaa aggagtgaag gacattcaaa aaccaactgc 120
 aataaaaaag ggtgacataa ttgctaaatg gagtggagga acagtgttta tcaattcttg 180
 attgggccac aatgatatac c 201

<210> 86
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)

<223> n = A,T,C or G

<400> 86

```

tttataaaaat attttatttta cagtagagct ttacaaaaat agtctttaa ataatcaaat      60
cccttttgca atataactta tatgactatc ttctcaaaaa cgtgacattc gattataaca      120
cataaactac atttatagtt gtttaagtcac cttgtagtat aaatatgttt tcattctttt      180
tttgtaataa ggtacatacc aataacaatg aacaatggac aacaaatctt attttgntat      240
tcttccaatg taaaattcat ctctggccaa aacaaaatta accaaagaaa agtaaaacaa      300
t                                                                    301

```

<210> 87

<211> 351

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(351)

<223> n = A,T,C or G

<400> 87

```

aaaaaagatt taagatcata aatagggtcat tgttgtcaca acacatttca gaatctttaa      60
aaaacaaaca ttttggtttt ctaagaaaaa gactttttaa aaaaatcaat tccctcatca      120
ctgaaaggac ttgtacattt ttaaacttcc agtctcctaa ggcacagtat ttaatcagaa      180
tgccaatatt accaccctgc tgtagcanga ataaagaagc aagggattaa cacttaaaaa      240
aacngccaaa ttcctgaacc aaatcattgg catttttaaa aagggataaa aaaacnggnt      300
aaggggggga gcattttaag taaagaangg ccaaggggtg tatgccngga c                351

```

<210> 88

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 88

```

gttttaggtc tttaaccaatt tgattgggtt atcaacaggg catgagggtt aaatatatct      60
ttgaggaaag gtaaagtcaa atttgacttc atagggtcatc ggcgtcctca ctctgtgca      120
ttttctggtg gaagcacaca gtttaattaac tcaagtgtgg cgntagcgat gctttttcat      180
ggngtcattt atccacttgg tgaacttgca cacttgaatg naaactcctg ggtcattggg      240
ntggccgcaa gggaaagggtc cccaagacac caaaccttgc aggggtacctn tgcacaccaa      300
c                                                                    301

```

<210> 89

<211> 591

<212> DNA

<213> Homo sapien

<400> 89

```

tttttttttt tttttttatt aatcaaataa ttcaaaacaa ccatcattct gtcaatgccc      60
aagcaccag ctggctctct cccacatgt cacactctcc tcagcctctc ccccaaccct      120
gctctccctc ctcccctgcc ctagcccagg gacagagtct aggaggagcc tggggcagag      180

```

ctggaggcag	gaagagagca	ctggacagac	agctatgggt	tggattgggg	aagagattag	240
gaagtagggt	cttaaagacc	cttttttagt	accagatatc	cagccatatt	cccagctcca	300
ttattcaaat	catttcccat	agcccagctc	ctctctgttc	tccccctact	accaattctt	360
tggctcttac	acaattttta	tccctcaaat	attcatccct	ggcccaacca	gtcccctgag	420
cctccctctg	gtggagactc	ctccacccat	gagctcccca	gagcatccaa	gacagagtgc	480
acagagacct	ggggaaggaa	gctgaacttt	gcagagatgt	ggacagggtc	aggctagggt	540
acagggtggt	ggtagaggag	acaagtttta	tttccaggcc	cacagtctct	c	591

<210> 90
 <211> 1978
 <212> DNA
 <213> Homo sapien

<400> 90						
tttttttttt	ttttttatca	aatgaatact	ttattagaga	cataacacgt	ataaaaataaa	60
tttcttttca	tcattggagt	accagatttt	aaaaccaacc	aacactttct	cattttttaca	120
gctaagacat	gttaaattct	taaatgccat	aatttttgtt	caactgcttt	gtcattcaac	180
tcacaagtct	agaatgtgat	taagctacaa	atctaagtat	tcacagatgt	gtcttaggct	240
tggtttgtaa	caatctagaa	gcaatctgtt	tacaaaagtg	ccaccaaaagc	attttaaaga	300
aaccaattta	atgccaccaa	acataagcct	gctataacctg	ggaaacaaaa	aatctcacac	360
ctaaattcta	gcagagttaa	cgattccaac	tagaatgtac	tgtatatcca	tatggcacat	420
ttatgacttt	gtaatatgta	attcataata	cagggttagg	tgtgtggtat	ggagctagga	480
aaaccaaagt	agtaggatat	tatagaaaag	atctgatgtt	aagtataaag	tcatatgcct	540
gatttcctca	aaccttttgt	ttttctctcat	gtcttctgtc	tttatatttt	tatcacaaac	600
caagatctaa	cagggttctt	tctagaggat	tattagataa	gtaacacttg	atcattaagc	660
acggatcatg	ccactcattc	atggttggtc	tatgttccat	gaactctaata	agcccaactt	720
atacatggca	ctccaagggt	atgcttcagc	cagaaagtaa	agggttgaaa	aagtagaaca	780
atacaaaagc	cctcgtgtgg	tgggaactgt	ggcctcactc	ttacttgtcc	ttccattcaa	840
aacagtttgg	cacctttcca	tgacgaggat	ctctacaggt	agggttaaaat	acttttctgt	900
gctattcagc	cagaaatagt	ttttgtgctg	gatatgattt	taaaacagat	tttgtctgtc	960
accagtgcga	aaacattaca	gatgtctggg	ctaatacaaaa	aacacataag	aatctacaac	1020
tttatattta	atactctatt	caaattttaac	tcaaagtaat	gcaaaataat	tagaagtaaa	1080
aacttaattc	ttctgagagc	tctattttgga	aaagcttcac	atatccacac	acaaatatgg	1140
gtatattcat	gcacagggca	aacaactgta	ttctgaagca	taaataaaact	caaagtaaga	1200
catcagttag	tagataccag	ttccagtatt	gggttaatgg	ctctggggat	cccattttta	1260
gcactctcag	atgaggatct	tgttcagttg	ttagactatc	attagtttga	ttaagcaact	1320
gaagtttact	tcataaatta	ctttttccta	tatccaggac	tctgcctgag	aaattttata	1380
cattcctcca	aaggtaagta	ttctccaaag	gtaagtattt	gactattaac	acaaaggcaa	1440
tgtgattatt	gcataatgac	actaaatatt	atgtggcttt	tctgttaggt	ttataagttt	1500
tcaatgatca	gttcaagaaa	atgcagatca	tatataacta	agggtttaca	ccagtgggtg	1560
acaaactatg	gcccacaggc	taaaccagc	ctccccctgt	ttttataaat	aagttttatt	1620
agacataacc	acactcattc	atctctgtat	tgtgtatagc	tgctttcacg	ctatactagc	1680
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<210> 91
 <211> 895
 <212> DNA
 <213> Homo sapien

<400> 91						
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<210> 92

<211> 1692

<212> DNA

<213> Homo sapien

<400> 92

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<210> 93

<211> 251

<212> DNA

<213> Homo sapien

<400> 93

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<210> 94

<211> 735

<212> DNA

<213> Homo sapien

<400> 94

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<210> 95

<211> 578

<212> DNA

<213> Homo sapien

<400> 95

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<210> 96

<211> 594

<212> DNA

<213> Homo sapien

<400> 96

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<210> 97

<211> 3101

<212> DNA

<213> Homo sapien

<400> 97

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<210> 98
 <211> 90
 <212> PRT
 <213> Homo sapien

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<400> 98
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Ala Thr Gly Pro Ala Asp Asp Glu Ala Pro Asp Ala Glu Thr Thr Ala
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Ala Ala Thr Thr Ala Thr Thr Ala Ala Pro Thr Thr Ala Thr Thr Ala
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<210> 99
 <211> 197
 <212> PRT
 <213> Homo sapien

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Ser Lys Arg Arg Val Arg Asp Lys Asp Gly Asp Leu Lys Thr Gln Ile
          35          40          45
Glu Lys Leu Trp Thr Glu Val Asn Ala Leu Lys Glu Ile Gln Ala Leu
          50          55          60
Gln Thr Val Cys Leu Arg Gly Thr Lys Val His Lys Lys Cys Tyr Leu
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Ala Ser Glu Gly Leu Lys His Phe His Glu Ala Asn Glu Asp Cys Ile
          85          90          95
Ser Lys Gly Gly Ile Leu Val Ile Pro Arg Asn Ser Asp Glu Ile Asn
          100          105          110
Ala Leu Gln Asp Tyr Gly Lys Arg Ser Leu Pro Gly Val Asn Asp Phe
          115          120          125
Trp Leu Gly Ile Asn Asp Met Val Thr Glu Gly Lys Phe Val Asp Val
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145 150 155 160
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 <211> 3410
 <212> DNA
 <213> Homo sapien

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<210> 101

<211> 553

<212> PRT

<213> Homo sapien

<400> 101

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Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly
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Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly
 65          70          75          80
Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile
 85          90          95
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Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly
115          120          125
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Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu
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Thr Cys Val Ala Ala Thr Leu Val Ala Glu Glu Ala Ala Leu Gly
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Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His
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Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg
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 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
 305 310 315 320
 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu
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 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg
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 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala
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<212> DNA

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